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THE CENTRAL CONNECTIONS OF THE VESTIBULAR PATHWAYS.

AN EXPERIMENTAL STUDY.

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OUR interest in the unsolved problems of Ménière's disease prompted this experimental investigation on the auditory nerves and cerebellum. The results following section of the vestibular nerves in animals are so different from those obtained in human beings that their transfer to man is impossible. Indeed, had the devastating effects of dividing the auditory nerve in dogs and cats antedated the operation on human beings[1a,b,c,d] the cure of Ménière's disease by this operative attack might well have been delayed.

Apparently there is no difference in the effects produced in dogs and cats except in degree, the cats reacting more severely. The operative attack upon the auditory nerves and the cerebellum was found to be much more difficult in both dogs and cats than upon human beings, largely because of the excessive vascularity about the dural sinuses in the posterior cranial fossa. Bleeding from this source is difficult to avoid, because the dura is so thin and so closely attached to the bone. By "rongeuring" the bone very cautiously and in very small amounts at each step, it is possible to separate the dura and stop effectively the bleeding by application of wax. The attack upon either the auditory nerves or the cerebellum is merely a matter of painstaking care. Without a bony defect of

adequate size the soft cerebellum quickly becomes edematous from the effects of trauma and thereby the interpretation of the results may be vitiated by the complications. This warning applies both to section of the auditory nerve and to the removal of the cerebellum. In hemisection the remaining half of the cerebellum may be damaged so severely as to be in large part necrotic. In partial or total section the brain stem may be injured. With either complication the experiment may be so defective that the results will be worthless.

In cutting the auditory nerve the bony defect must be made so far laterally that the cerebellum may be retracted without trauma. Hemisection of the cerebellum is done by splitting the vermis from the tentorium anteriorly to the membranous covering of the apex of the fourth ventricle; this is practically bloodless. The hemisphere then is turned outward and upward until the large peduncle is isolated. This is transected with a scalpel; the cerebellar lobe has only minor attachments along the upper margin of the fourth ventricle. Midsection of the vermis makes either unilateral or total removal of the cerebellum much simpler and practically devoid of trauma to the remaining structures.

Section of the restiform body (middle peduncle) in animals dates back nearly a century. Vulpian[8] (1866) refers to Magendie's experiments in sectioning the middle peduncle of the cerebellum in cats; rotation of the animal with incredible rapidity followed and to the same side. His results were confirmed by Vulpian, Schiff, Hitzig[6] and other great physiologists working about the middle of the nineteenth century. The results were the exact equivalent of destruction of the semicircular canals (Flourens' experiments). Ferrier[3] (1880) and Ferrier and Turner[4] (1898) divided the auditory nerve in rabbits and monkeys; their results were similar to those following section of the restiform body. They refer to earlier experiments of this type by Brown-Sequard. In the course of time the rolling movements subsided and the animals walked again, but in a sprawling, unsteady fashion. Ferrier[3] comments upon the great mortality attending his attempts to expose the cerebellum in dogs and cats: he "succeeded in comparatively few," but the results were the same as in rabbits.

In recent years, Fulton, Liddell and Rioch[5] (1930) sectioned the auditory nerve in cats with greater ease and with more assurance that contiguous structures have not been injured. Their results, however, are not different and were identical with labyrinthectomies. They stress the advantage of "dial" (a barbiturate) anesthesia in facilitating the operative procedure, and doubtless the prolonged anesthesia (36 hours or longer) is responsible for the fact that their animals usually survived and after a period of 9 to 13 days walked again, at first in a very poor sprawling fashion, but gradually improving. Owing to the short duration of ether anesthesia all our

animals succumbed within 48 hours, the period in which the severity of the whirling movements is at its maximum. After 36 hours it was found that these movements steadily diminished. This was the experience of Ferrier and Turner and later of Northington and Barrera[7] (1934) and of Dow[2] (1938) in monkeys. This also corresponds fairly well with the subjective rotary effects in man following the section of the vestibular nerves. Dow has emphasized the fact that the severity of this disturbance decreases as one ascends the phylogenetic scales. He even found that the effects produced by destruction of the labyrinth in anthropoids (baboons and chimpanzees) were less than in monkeys. Ferrier[3] dwells at some length on the shift from the actual rotation of the body in animals, including monkeys, to the purely subjective visual disturbance that attends lesions of the auditory nerve in human beings. At that time the auditory nerve had, of course, not been sectioned in man.

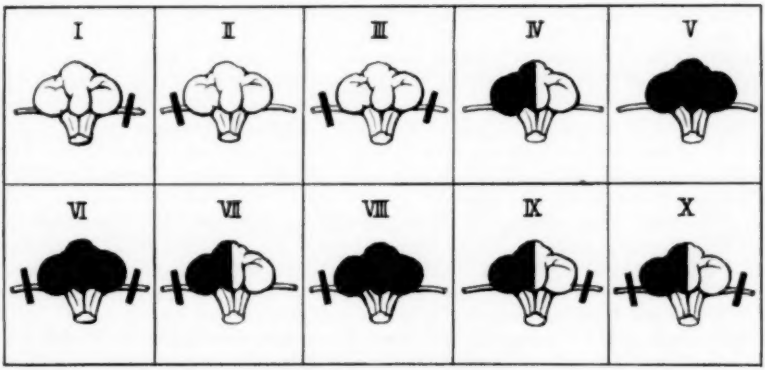

FIG. 1.—Tabulation of experiments.

Our results following section of the auditory nerves in animals are in complete accord with those of all other experimentalists on this line. We are, however, less concerned with these effects than with the central pathways of vestibular function which we believe are concentrated almost entirely in the cerebellum. This view was expressed by Meynert (see Ferrier[3]), but he apparently also believed that the same was true of the auditory pathways, an utterly untenable concept, according to Ferrier, because his experiments had led him to the conclusion that a center for hearing was located in each temporal lobe—a view, by the way, that modern cerebral excisions have rendered impossible, at least in human beings.

Experiments. In order to avoid repetition only one protocol has been entered for each experiment, although each has been repeated at least once.

I. *Adult Cat.* Section of right eighth nerve (N VIII) (cerebellar approach); ether, November 15, 1934. The animal stood the operation well; 6 hours later it was awake and nervous. There was facial paralysis on the

right. It lay against the side of the cage on the right side. Placed on the floor it rolled violently to the right, spinning until it finished exhausted against the wall. If placed on the left side, it immediately rolled over and over, but always to the right. It could not stand or walk. Nov. 16: Same reactions. Unable to eat or drink and is fed by tube. Nov. 17: Died. Autopsy showed total section of the right seventh and eighth nerves.

II. *Adult Cat.* Total section of eighth nerve left; ether, November 15, 1934. Exactly the same reactions, except whirling is to the left. Unable to stand or walk.

III. *Adult Cat.* Bilateral section of eighth nerve (cerebellar approach); ether, December 3, 1935. Cat in good condition at end of operation. Six hours later it was awake and lying against the side of the cage. Both sides of the face were paralyzed. It did not respond to noises. Placed on the floor it rolled violently to the right, at other times to the left. It was unable to sit, stand or walk and would not take water or food. Dec. 4: Same reaction as before. Dec. 6: Died. Autopsy showed total section of both seventh and both eighth nerves.

III. (*a*) *Adult Dog.* Section of nerves VIII, bilateral (cerebellar approach); ether, February 14, 1935. Animal stood operation well. Five hours later marked nystagmus; rolled and spun violently to either side, but not as violently as the cat. Unable to stand, sit or walk. Died following day. Necropsy showed both auditory nerves totally divided.

IV. *Adult Cat.* Removal of left half of cerebellum; ether, January 21, 1935. Six hours later cat awake and quiet. No turning movements and no rolling at any time. Lay on left side; could not sit up or stand.

V. *Adult Cat.* Removal entire cerebellum, January 10, 1935. Cat remained quiet, did not whirl at any time. Could maintain sitting position, but could not stand or walk.

VI. *Adult Cat.* Removal entire cerebellum and section of both nerves VIII; ether, January 14, 1935. Animal stood the operation well. Six hours later it was awake, lying on right side. Gave no evidence of hearing noises. For most part animal was limp and unable to stand; it remained on either side or back when so placed. When picked up by hind quarters with head and front of body hanging, it executed normal movements (coördinated) of forelegs and turned head from side to side. Jan. 15: Same reactions as yesterday. Will not eat or drink. Jan. 17: Died. Autopsy showed complete extirpation of cerebellum and both eighth nerves were totally divided.

VII. *Adult Cat.* Removal *left half* cerebellum and section nerve VIII *left;* ether, January 17, 1935. Six hours later animal in good condition. Placed on floor it turned and rolled violently *to the left,* coming to rest on the left side. Movements began with turning of head to *left* and then body was rapidly turned. Died following day. Remaining half of cerebellum showed no necrosis; eighth nerve had been totally divided.

VIII. *Adult Cat.* Section left nerve VIII and left half of cerebellum removed; ether, January 17, 1935. It has since been whirling to the left. Jan. 18: Removed the remaining right half of the cerebellum. Six hours later the cat was awake, quiet and without turning movements. Lay quietly on either side. Picked up by hind quarters, it turned normally either to right or left; moved both forelegs in normal manner. Died the following day. Autopsy showed all cerebellum removed; left auditory nerve was totally divided. Brain stem showed no softening.

IX. *Adult Cat.* Section right nerve VIII and removal of left half of cerebellum; ether, January 30, 1935. Five hours later it was wide awake. Nystagmus present. It lay on the left side in the cage, tried to push itself about but *did not spin.* Regardless of position and movements induced, no

whirling movements could be provoked. When picked up and put on right side it lay quietly. There was a striking contrast to the cats with the cerebellum intact, or with half of cerebellum removed and the ipsolateral nerve VIII sectioned. Movements of all extremities were good. Jan. 31: Same reactions as yesterday. No spinning movements. Feb. 1: Reactions unchanged; it died during the night. Autopsy showed nerve VIII sectioned on right. Right half of cerebellum was in good condition.

X. *Adult Cat.* Section under ether of both nerves VIII and removal left cerebellar lobe, October 18, 1936. Awake 3 hours later, had nystagmus. Rolled violently to the *left* until exhausted. Lay on the right side. Oct. 19: similar violent whirling to *left* only. Died during night. Autopsy showed total division of both eighth nerves and an intact right cerebellar lobe.

TABLE 1.—RESULTS OF EXPERIMENTS.

	Operation.	*Result.*
I.	Total section *right* N VIII	Violent whirling to right; cannot stand or walk.
II.	Total section *left* N VIII	Violent whirling to left; cannot stand or walk.
III.	Total section *both right and left* N's VIII	Violent whirling to both sides; cannot stand or walk.
IV.	Removal *left* half of cerebellum	*No* whirling; cannot stand or walk.
V.	Removal entire cerebellum	*No* whirling; cannot stand or walk.
VI.	Removal *entire* cerebellum and total section of both N's VIII	No whirling; cannot stand or walk.
VII.	Removal *left* half of cerebellum and total section *left* N VIII	Violent whirling to *left;* cannot stand or walk.
VIII.	Removal *entire* cerebellum and total section *left* N VIII	*No* whirling; cannot stand or walk.
IX.	Removal *left* half of cerebellum and total section right N VIII	No whirling.
X.	Removal *left* half of cerebellum and total section both N's VIII	Violent whirling to left.

Summary and Conclusions. A summary of the above experiments in terms of whirling indicates the following:

1. Section of either N VIII results in frequent spells of violent whirling—always rolls to the side of the lesion (Experiments I and II).

2. Section of both N's VIII results in violent whirling—turns to either side (Experiment III).

3. After removal of one-half of the cerebellum there are no rotary movements (Experiment IV).

4. After removal of the entire cerebellum there is no whirling (Experiment V).

5. After section of N VIII and removal of the cerebellar lobe of the same side, violent rotation follows; and the whirling is to the same side (Experiment VII).

6. After section of one N VIII and removal of the opposite cerebellar hemisphere no whirling results (Experiments IX and X).

From these experiments it will be seen that the ability to sit or stand or walk is completely lost immediately after section of either or both auditory nerves, and as far as we can tell the result is, in

this respect, exactly the same as removing either half or all of the cerebellum. The great difference following these two procedures is that after removal of half or all of the cerebellum the animal lies quietly, whereas after section of one or both auditory nerves a terrific whirling of the body results and continues until death results from exhaustion. Fulton, Liddell and Rioch[5] have shown that after section of one or both auditory nerves under prolonged "dial" anesthetic the severe period may be passed under the anesthetic. When the animal responds after 36 to 48 hours, the rotation is so much less severe that the animal will recover.

The profound effects produced by sectioning one or both auditory nerves are entirely different from those in man.[1a,b,c,d] The body itself is set in motion in a series of violent whirling movements that are precipitated by any slight movement of the body and always occur to the side of the sectioned nerve, or to either side when both nerves are cut. These violent whirling attacks are immediately abolished when the entire cerebellum is removed.

In man, the body itself does not rotate following section of a vestibular nerve, but the effect is one of rotation of objects in the room, or when the eyes are closed of rotation of the body. In man, therefore, the aberrations of vestibular function are transferred to, and translated by, the visual tracts so that the effect produced is *subjective* and visual; in animals, the untoward effect is somatic and objective. Doubtless the transfer of the vestibular function from the cerebellum in dogs and cats to the visual tracts in human beings is related to a lessened importance of the semicircular canals in man as compared to animals.

In keeping with this change in the functional setup of the vestibular pathways, it is interesting that section of *both* eighth nerves in *man* has little, if any, effect upon the equilibrium of the body, but rather the effect is one of jumbling the appearance of objects when the body is in motion, *i. e.*, the effects are upon ocular coördination. These physiologic effects, therefore, indicate the probability that when the vestibular pathways can be accurately charted, those in dogs and cats will predominantly pass to the cerebellum, whereas those in human beings will pass up the brain stem to the centers controlling the extraocular movements.

The fact that the violent rotary movements of the body are instantly and permanently abolished (in dogs and cats) when both cerebellar lobes are removed doubtless indicates that the central apparatus concerned with equilibrium is very largely, if not entirely concentrated there.

Another striking and perhaps surprising feature of the experiments is the contralateral relationship between the cerebellum and the peripheral vestibular tracts, *i. e.*, bodily rotation after section of an eighth nerve is unaffected by removal of the ipsolateral half

of the cerebellum, but is abolished by removal of the contralateral half. This can only mean that the vestibular pathways decussate like the pyramidal tracts.

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THE VALUE OF COLLOIDAL ALUMINUM HYDROXIDE IN THE TREATMENT OF PEPTIC ULCER.

A Review of 407 Consecutive Cases.

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The treatment of peptic ulcer by the continuous administration of colloidal aluminum hydroxide has now been in use for 3 years. A review of 407 cases in which this method of therapy has been employed furnishes a sound basis for a reëxamination of principles, and for revaluation of results. This treatment represents no radical departure from the methods that have been in use for many years, all of which have been designed to counteract the effects of excessive acid secretion in the stomach. The drip treatment with colloidal aluminum hydroxide merely emphasizes and expands this principle by the use of a more effective neutralizing agent, administered continuously instead of intermittently.

It has been amply proved by clinical and experimental evidence that hydrochloric acid is active, not only in initiating ulcerations of the stomach and duodenum, but also in preventing their healing. The process of repair which consists of deposition of granulation tissue, begins almost coincidentally with formation of an acute peptic ulcer. The corrosive action of hydrochloric acid is the most formidable antagonist to this healing process. If the factors causing the ulcer are dominant over the natural healing process, the lesion progresses steadily, and in time becomes chronic. On the other hand, if the factors producing the ulcer are satisfactorily controlled, then the balance shifts in favor of healing. It follows that treatment, to be satisfactory, should protect the ulcer from acid corrosion continuously, not only during the day, but also throughout the night.

Otherwise, the accumulation of acid at night may destroy some of the granulation tissue formed during the day, and thus delay or prevent healing.

Rationale of Treatment. Although alkaline powders have been, and still are being widely used in the treatment of peptic ulcer, the results obtained with them are not always satisfactory. Their neutralizing effect, which is short-lived, is followed by a marked compensatory stimulation of acid secretion in the stomach. Crohn and Reiss[1] have demonstrated that magnesium oxide, sodium bicarbonate, and so on, are the most powerful known excitants of gastric secretion, aside from histamine. Sodium bicarbonate has the additional disadvantage of liberating carbon dioxide gas, which, if it cannot escape within a few minutes, may accumulate in sufficient quantity to be a potential danger through perforation of an ulcer. Furthermore, the administration of large quantities of alkalies may present potentially the hazard of alkalosis.

It is obvious that the ideal agent for the treatment of peptic ulcer is one that will neutralize hydrochloric acid without producing any general systemic reaction, and without disturbing the secretory or motor function of the gastro-intestinal tract. Colloidal aluminum hydroxide meets these qualifications.

Characteristics of Colloidal Aluminum Hydroxide. Colloidal aluminum hydroxide is a white, gelatinous substance, mildly astringent and non-irritating. It is amphoteric, with a pH of 6.9; hence it may be administered continuously without danger of alkalosis. The preparation contains about 5% of aluminum hydroxide and about 0.6% of sodium chloride; the remainder is water.

Experiments *in vitro* demonstrate that this colloidal product, when undiluted, combines with 12 times its volume of tenth-normal hydrochloric acid within half an hour. It is non-toxic and has no harmful effect, even in large doses. Large quantities of colloidal aluminum hydroxide do not disturb the acid-base balance of the blood, as shown by estimations of the blood chlorides, the carbon dioxide-combining power, and the pH of the blood. There is practically no absorption of aluminum from the gastro-intestinal tract, as shown by Ivy,[3] in dogs, and by Einsel, Adams, and Myers,[2] in man.

Besides its exceptional antacid action, colloidal aluminum hydroxide has the additional advantage that it protects the ulcer by coating it with a jelly-like mass. This adherence to the walls of the stomach can be shown roentgenographically, after the substance is mixed with a small quantity of barium.[5c] Numerous investigators, including Ivy and his collaborators,[3] have reported that in animals receiving preparations of aluminum hydroxide, necropsy frequently shows the mucosa of the stomach and duodenum coated with the material so that it appears as if covered with flour paste.

The astringent action of colloidal aluminum hydroxide is also advantageous in healing the ulcer, and in arresting hemorrhage in bleeding ulcer. Sollmann[4] has pointed out that "astringents are used therapeutically to reduce inflammation of mucous membranes, promote healing, and to arrest hemorrhage (by coagulating the blood)."

With such a neutralizing agent, which effectively combats acidity, and is absolutely non-toxic, it is safe to make practical application of the principle that the ulcer should be constantly and continuously protected from the corrosive effect of hydrochloric acid. Such treatment abets the natural healing process in its struggle against the antagonistic effect of acidity. To be entirely successful, not more than 1 hour can be allowed to elapse without medication. The treatment must be continued throughout the night, lest the delicate granulation tissue formed during the day be destroyed by accumulation of acid. The granulation bud is extremely friable and easily destroyed, and the ulcer must be protected until sufficient tissue has been deposited to fill in the crater. According to roentgenographic studies, this requires 7 to 10 days.

The same method has been used successfully in the treatment of bleeding ulcers.[5a] Because of its astringent effect, colloidal aluminum hydroxide hastens the coagulation of blood. The danger in hematemesis, however, arises not so much from a single episode of bleeding, but because of the likelihood of its recurrence. The hemorrhage from a blood-vessel in the stomach usually ceases as suddenly as it begins, when the bleeding point is plugged with fibrin. Destruction of this fibrin clot by acid digestion is the cause of recurrence of the bleeding. Thus the purpose of the continuous administration of colloidal aluminum hydroxide in hematemesis is to promote clot formation and then to protect the delicate fibrin from the action of strong unbuffered gastric juice.

That colloidal aluminum hydroxide does actually prevent digestion of the fibrin clot can be demonstrated experimentally *in vitro*. A clot of blood placed in a test tube filled with freshly aspirated gastric juice, and placed in an incubator at 37° C. shows evidence of digestion within 1 to 2 hours. However, when colloidal aluminum hydroxide is added to the tube containing the gastric juice and a small clot of blood, there is no evidence of digestion after 24 hours. Pepsin is not active in alkaline or neutral solutions.

Technique of Treatment. *Administration by Drip Apparatus.* The technique of administrating colloidal aluminum hydroxide by the drip method has been described previously.[5a,6a,b] This method of treatment requires hospitalization of the patient. The colloidal aluminum hydroxide, diluted to 25%, is continuously instilled into the stomach through a nasogastric tube at the rate of 15 drops per minute, both day and night, for 10 days. The flow of the drops is regulated and controlled by a special apparatus.

The indwelling nasal catheter was the source of considerable difficulty in some of the early cases. When a No. 12 Levin tube was used, the lumen was so small that it would become occluded by particles of food regurgitating back into the tube, or by coating of the walls by the aluminum hydroxide itself. This, of course, caused cessation of the flow, and necessitated troublesome irrigations of the tube, which corrected the difficulty only temporarily, and therefore had to be repeated frequently. When a large Levin tube was used, many of the patients complained of soreness in the nose and throat, even when the tube was well lubricated with mineral oil, and frequently they would remove the tube themselves when the discomfort became too great.

These difficulties were overcome by using a soft collapsible thin rubber tube about $\frac{1}{4}$ inch in diameter, passed through the nose into the stomach with the aid of a silkworm-gut suture.[5b] This acts as an obturator and is left in place within the tube to prevent its kinking. This tube has entirely eliminated the difficulties of obstruction of the lumen and discomfort to the patient experienced with the Levin tube. The nasogastric tube is passed only as far as the lower end of the esophagus. This precaution eliminates the rare possibility of any danger of trauma to the lesion.

Oral Administration. In the few instances in which patients objected to or could not tolerate the nasogastric tube, the medication was administered by mouth. One ounce of a 25% suspension of colloidal aluminum hydroxide in water is given every hour during the day until the patient retires, and then he is awakened every 2 hours during the night to receive the same dose. Usually a sedative is administered in the evening, so that the patient falls asleep promptly after being aroused for the medication. With the drip method, of course, the patient rests all night without interruption.

Diet and Supplementary Medication. Along with this treatment in the hospital, the patient receives a bland diet of which small quantities are taken every 2 hours for 12 hours. This consists of milk with one-third cream, cooked cereal (oatmeal, farina and cream of wheat), a soft boiled egg, a slice of toast, butter, cream soups, gelatin, custard, tapioca, and junket. Inasmuch as the astringent action of aluminum hydroxide causes some constipation, mineral oil is given daily, or enemas every other day. A sedative is administered each night to prevent worry about the treatment.

The Treatment of Massive Hemorrhage. The same regimen is employed in cases of hematemesis and melena. As soon as the patient with melena is admitted to the hospital, a soft nasogastric tube is passed through the nose to the cardiac end of the stomach, and the drip treatment is begun. If hematemesis is present, the patient receives colloidal aluminum hydroxide by mouth every hour until vomiting has ceased; then the drip treatment is begun.

These patients receive food every 2 hours, and the diet is the same as that administered to other patients with peptic ulcer. To induce rest, the hypodermic administration of sodium phenobarbital is preferred to that of morphine, because morphine not only interferes with the normal function of the gastro-intestinal tract, but also has the undesirable effect of causing emesis, in some instances.

Small transfusions, usually about 250 cc. of blood, are given when the systolic blood pressure is reduced to less than 90, or when the hemoglobin is below 30%.

Ambulatory Treatment Following Hospital Care. When the course of treatment in the hospital is completed, an ambulatory regimen is continued for 30 days after the patient leaves the hospital, before the healing of the ulcer is considered complete. When the ulcer crater has become filled in

with granulation tissue, which is shown on the roentgenogram by disappearance of the niche, the lesion may still not be healed. It may take more time for the mucosa to grow around the periphery toward the center. Hence this area must be protected against the harmful action of hydrochloric acid, until complete healing, with epithelization, has taken place. Even if the lesion were healed, the regenerated mucous membrane is thin and deformed, and implanted on dense fibrous tissue, with imperfect blood supply, and therefore would require the same protection.

The patients are advised to take 2 teaspoonfuls of aluminum hydroxide in 2 ounces of water every 2 hours until bedtime, and mineral oil at night, along with a convalescent ulcer diet. This diet is limited in quantity, and avoids mechanical, chemical and thermal irritation. In addition to the foods allowed in the hospital, it includes puréed vegetables, stewed fruits, stewed chicken, creamed fresh fish, cottage or cream cheese, rice and macaroni.

Even when the ulcer is completely healed, the underlying diathesis which produced it in the first place still remains, and consequently it is likely to recur. A patient with peptic ulcer should be taught to understand, and to accept the fact that, since the disease is caused by some fundamental physiologic disturbance as yet not well understood, the physician cannot promise permanent cure of the disability. The best that can be offered is to heal the existing ulcer, and to try to prevent recurrence by diet and medication.

Results of Treatment.—In a period of 3 years from September, 1935, to October, 1938, 407 patients with peptic ulcer were treated with colloidal aluminum hydroxide on the medical service at St. Luke's Hospital. In this group, there were 322 men and 85 women. There were only 8 negroes in the group; 399 were white persons.

Approximately 25% of these patients (101) were suffering from acute massive hemorrhage at the time of admission. In 8 patients with hematemesis, the situation of the ulcer could not be determined. There were 285 cases of duodenal ulcer and 83 of gastric ulcer. Twenty-two patients had ulcers in both the stomach and duodenum, and 9 had marginal ulcers (6 of these followed gastro-enterostomy, and 3 followed gastric resection).

The continuous drip method was used for 270 patients, while 86, who were unable to tolerate the nasogastric tube, received the medication orally. Fifty-one patients received colloidal aluminum hydroxide by both the continuous drip method, and orally. In these instances, the nasogastric tube could not be tolerated for the entire period of treatment, and the remainder of the course was given by mouth.

The most striking features of the treatment of peptic ulcer by the continuous administration of colloidal aluminum hydroxide are: 1, the prompt relief of pain, 2, the rapid healing of the ulcer, 3, the healing of refractory ulcers, and 4, the excellent results in cases of massive hemorrhage.

Prompt Relief of Pain. Patients who have had severe pain, and have obtained only temporary relief by diet and alkalies, have

noticed a complete disappearance of pain during the first 24 hours of treatment, and some immediately after it was started.

Rapid Healing of the Ulcer. Roentgenographic studies showed disappearance of the niche in the majority of cases of gastric ulcer at the end of 10 days; in some, as early as 7 days. A longer time, usually about 14 days, was required for filling in the crater of large ulcers. It is much more difficult to demonstrate evidence of healing in cases of duodenal ulcer because the niche so often is not visible roentgenographically in this type. Hence it is necessary to judge the results of treatment of duodenal ulcers on the basis of symptoms and follow-up examinations.

Gastric ulcers frequently heal without a trace, and only occasionally produce an hour-glass deformity. Duodenal ulcers leave a scar deforming the duodenum. The typical niche produced by an ulcer is difficult to demonstrate on a roentgenogram of the duodenum. Even if the niche is found before treatment, its absence after treatment may not mean that the ulcer has disappeared, but merely that the second roentgenogram does not show it. To make the interpretation still more difficult, a healed ulcer in the duodenum may still produce a niche. In 1 case in this series, a large duodenal niche remained after two courses of treatment with aluminum hydroxide, and the patient was sent to surgery for a gastric resection. Exploration revealed that the ulcer was healed, and entirely covered with newly formed mucosa. In another instance, the patient was operated upon elsewhere for the same reason. The attending surgeon reported that the ulcer was healed. These are the only cases, according to the records, in which operation has been performed following the treatment with colloidal aluminum hydroxide.

Healing of Refractory Ulcer. Many of the patients in this group had tried other forms of treatment without experiencing any improvement, and yet have responded rapidly to the drip treatment. Apparently, in the cases of so-called refractory ulcer, the previous failure to heal was due to the accumulation at night of acid which destroyed some of the newly formed granulation tissue. When the medication was applied continuously, both night and day, these same ulcers healed very rapidly.

One patient with a duodenal ulcer had been in bed for 6 weeks on a Sippy diet, plus alkalies, but had received no treatment during the night; he had displayed no improvement at the end of that period. A gastric resection had been advised by his physician, but he decided to try the continuous drip treatment with colloidal aluminum hydroxide instead. After 10 days of treatment, he was free from symptoms and the duodenal cap showed less deformity on the roentgenogram. Other patients have also been spared from operation by this treatment.

In another patient who had had a gastric resection, a large ulcer crater developed at the margin. He was put to bed for 4 weeks on a

Sippy diet, with alkalies; at the end of that period the crater was still present. He then took the continuous drip treatment, and at the end of 10 days, several roentgenograms were made, and they showed a complete disappearance of the ulcer crater.

In 4 cases in which the usual clinical response was lacking, and in which the roentgenographic appearance of large ulcer craters was not altered by the drip treatment, the patients were operated upon, and were found to have malignant lesions. These cases are not included in the present series, since the treatment functioned merely as a therapeutic test for malignancy.

Massive Hemorrhage. From September, 1935, to October, 1938, 101 patients with hematemesis or melena have been treated with colloidal aluminum hydroxide. In this series, there have been but 3 deaths. It is interesting to contrast this mortality rate of 3% with that observed at the same hospital in the 5-year period preceding the inauguration of this form of medical treatment. During that time, there were 38 cases of massive hemorrhage from the gastrointestinal tract, with 11 (29%) deaths.

This group includes only those patients who were admitted as emergency cases for the treatment of massive hemorrhage as the leading, often the only symptom. They were vomiting bright red or dark blood, or had bloody or tarry stools, along with secondary anemia sufficient to produce weakness, pallor, dyspnea or rapid pulse. Patients with blood-streaked or occasional "coffee-grounds" vomitus, occult blood in the stool, or rare tarry stools were not included in this group.

Fifty-six patients had hematemesis, 45 had melena. Sixty-seven had duodenal ulcer; 19 had gastric ulcer; 4 had both types. There were 3 with marginal ulcers (2 following gastro-enterostomy, and 1 following gastric resection). In 19 cases, there was no history of ulcer. In 8, the situation of the lesion could not be found.

The drip treatment was given in 57 cases; 19 patients received the medication orally, and in 14, colloidal aluminum hydroxide was given by both methods.

The 3 patients who died were all white men, aged 45, 51, and 56 years, respectively. The first patient had had a duodenal ulcer for 7 years, and had been vomiting blood for 2 weeks before admission. The drip treatment was administered for 12 days, during which time he had two transfusions. Death occurred following a severe hemorrhage on the twelfth day. Necropsy revealed a chronic duodenal ulcer, 1 cm. in diameter, with a large artery (gastro-duodenal artery) protruding from its base.

The second patient, aged 51 years, gave no history of an ulcer but had been vomiting considerable blood for 2 days before admission. He received colloidal aluminum hydroxide orally for 5 days, during which time he had two transfusions. This patient died on the sixth day, and autopsy revealed a superficial ulcer on the posterior

wall of the stomach, about 1.5 cm. in diameter. Projecting from one end was a large vessel (a large branch of the left gastric artery), about four-fifths of which had undergone necrosis. There was also evidence of generalized arteriosclerosis.

The last patient, aged 56 years, had complained of epigastric distress for about 3 months, and had severe hematemesis at the time of admission. He received colloidal aluminum hydroxide orally for 3 days and two transfusions. He died on the fourth day. It had been impossible to obtain a roentgenogram of this patient's stomach, and permission for an autopsy was not obtained.

It is interesting to note that from September, 1935, to November, 1937, 54 consecutive cases of massive hemorrhage were treated by this method, without a single death. The 3 deaths occurred within a period of 48 days, the first, November 8, 1937, the second, December 6, 1937, and the third, December 26, 1937. Since then, 44 additional cases have been treated, without a death.

A hemorrhage in a person more than 45 years of age may be an indication for surgery, especially when the vessels are sclerotic; on the other hand, there is a fair chance that the patient may never have another episode of bleeding. A single hemorrhage in a person less than 45 years of age is definitely not an indication for operation, but repeated hemorrhage may be.

Surgical intervention in gastric hemorrhage entails great risks. If the bleeding is caused by an acute peptic ulcer, operation is likely to be futile, because there is no external indication of the presence of an ulcer, and the stomach must be opened to deal with the bleeding point. The search for this is so difficult that the ulcer often is not found. In such instances, the shock of the operation, in addition to the prolonged hemorrhage, is almost certain to result in the death of the patient. On the other hand, a chronic ulcer is easily found. However, even in the presence of a known chronic ulcer, operation is inadvisable, because the chronic ulcer may not be the source of the hemorrhage. It is impossible to exclude in such cases a complicating acute ulcer which would probably never be found at operation. Exsanguinated patients, even when they receive blood transfusions, are poor surgical risks.

Recurrences. It is impossible to estimate accurately the number of recurrences following any type of treatment for peptic ulcer. Patients who suffer from this disease characteristically are nervous and high strung. Consequently they are impatient and restless and in some cases not so coöperative with their physician as they should be. They resent the chronicity of their illness and the prolonged treatment which it requires and are always seeking the physician who will promise them a quick and permanent cure.

The occupations and environments of many of these patients subject them to great nervous strain which undoubtedly aggravates the severity of their symptoms. Consequently the physician often

advises the patient to change his environment and method of living if he wishes to obtain relief from peptic ulcer. This advice is excellent in theory but, in my experience, can seldom be applied in practice.

Knowing that, for economic reasons, the majority of patients with peptic ulcer are going to continue to be subjected to work and worry that induce nervous strain, and that there is little or nothing that they can or will do about it, it is necessary to offer them medication which will counteract the consequences of the tension of modern living.

Apparently all peptic ulcers begin as acute lesions and possess originally a strong tendency to heal. Frequently, however, they are prevented from doing so by certain peculiar influences to which they are subjected. Hyperacidity can convert an acute ulcer into one of the chronic type, as has been shown experimentally. It follows that, if the acidity of the stomach could be controlled absolutely, and for an indefinite period of time, the recurrence of a chronic peptic ulcer should be prevented.

Since peptic ulcer is, in most cases, a chronic disease, it requires prolonged treatment. After the course in the hospital, and the ambulatory regimen for 30 days thereafter, the patient is advised to take 2 teaspoonfuls of colloidal aluminum hydroxide after each meal, and at bedtime. The stringency of the diet is relaxed somewhat, but the patient is warned to avoid coarse food and condiments and to eschew alcohol and tobacco.

It has been impossible to keep in touch with all the patients who received the intensive course of treatment with colloidal aluminum hydroxide in the hospital. However, 30 have been followed closely for 2 years or more (4 for 3 years), in order to determine whether the prolonged administration of colloidal aluminum hydroxide would prevent the recurrence of peptic ulcers. All of them have taken colloidal aluminum hydroxide regularly during this period. Twenty-six in the group had duodenal ulcer, and 4 had gastric ulcer.

The patients reported once a month for examination and advice. At the end of 2 years, none had had any recurrence of symptoms, and roentgenograms showed no evidence of new lesions in the stomach or duodenum. Several of these patients, prior to the treatment, had had a recurrence of symptoms about two or three times annually for a number of years.

It is to be noted, however, that since these patients were examined so regularly, they were being continually reminded to adhere to the recommended diet, and this factor cannot be overlooked in considering their freedom from recurrences. On the other hand, some of them had been conscientious and meticulous previously in following dietary and other prescribed treatment, and still had not been free from ulcer symptoms for a comparable period.

To determine whether daily doses of colloidal aluminum hydrox-

ide given over such a prolonged period produced any undesirable effect, complete laboratory studies were carried out on each of the 30 patients. The blood was analyzed for chlorides and carbon dioxide-combining power; no disturbance of the acid-base balance of the blood was indicated. Gastric analysis with histamine showed that the gastric acidity was approximately normal in all cases. Sigmoidoscopic examination of each patient showed no evidence of irritation of the lower bowel. The urinalysis showed no deviation from normal.

Summary. An experience in the management of peptic ulcer by means of the continuous administration of colloidal aluminum hydroxide extending over 3 years, and including the treatment of 407 patients, furnishes convincing evidence that this method has definite advantages over other forms of therapy in this disease. The treatment represents no radical departure from previous methods, but controls gastric acidity more effectively because of the use of a more efficacious neutralizing agent, which is administered continuously instead of intermittently. By the continuous administration of colloidal aluminum hydroxide, both day and night, the delicate granulation tissue formed in the process of healing is not destroyed by accumulation of acid. In addition to its exceptional neutralizing effect, colloidal aluminum hydroxide appears to promote healing by coating the lesion with a jelly-like, protective mass, and by its astringent effect.

The most striking features of this treatment are: 1, the prompt relief of pain in all cases (within 24 hours); 2, the rapid healing of the ulcer (in 7 to 10 days, according to roentgenograms); 3, the healing of refractory ulcers in patients who had tried other methods of treatment, without success; and 4, the excellent results in cases of bleeding ulcer. Of 101 patients with massive hemorrhage treated, only 3 died.

It is not claimed that this regimen can prevent the recurrence of ulcers, after they have been healed. Nevertheless, 30 patients who have continued to take colloidal aluminum hydroxide by mouth for 2 years or more, have been followed closely throughout the entire period, and none of them has had a recurrence, although a number of them previously had had an exacerbation of ulcer symptoms two or three times annually, for several years. Laboratory studies made on these patients showed that the drug had no harmful effect, even when administered for prolonged periods.

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FIG. 1.—Case 1. An ulcer niche defect and spastic constriction of the lower esophagus is shown at arrow *A*, the herniated cardia of the stomach at *B*, and the diaphragm at *C*.

FIG. 2.—Case 2. An ulcer niche defect and spastic contraction of the lower esophagus is illustrated at arrow *A*, the herniated cardia of the stomach at *B*, and the diaphragm at *C*.

PEPTIC ULCER OF THE LOWER ESOPHAGUS ASSOCIATED WITH ESOPHAGEAL HIATUS HERNIA. REPORT OF 2 CASES.

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Diaphragmatic hernia of the cardia of the stomach through the esophageal opening occurs with greater frequency than a review of the literature would indicate. Numerous reports of this subject abound in the more recent literature. The incidence of esophageal hiatus hernia vary from 0.02 to 1.2%.[2] This form of hernia may be complicated by anemia hemorrhage, diverticula of the esophagus, cardiospasm, stricture of the esophagus, peptic ulcer of the esophagus, carcinoma of the esophagus or stomach, gastric and duodenal ulceration.

The coëxistence of gastric ulcer with esophageal hiatus hernia has been reported in many instances. However, a large number of cases of unexplained anemia, associated with this condition are recorded, many of which have been explained as being due to congestion. Bock, Dulin and Brooke report 10 cases of secondary anemia associated with hiatus hernia, 3 of which had abdominal explorations and 2 others came to autopsy. They found no lesions to account for the bleeding, except a marked congestion of the mucous membrane, caused by increased venous pressure.

In this communication, 2 cases of peptic ulcer of the esophagus associated with esophageal hiatus hernia are presented. In perusing the available literature, I have been unable to find a similar report of the coëxistence of peptic ulcer of the esophagus and hiatus hernia.

Case Reports. Case 1.—Mrs. I. B. H., aged 46, complained of difficulty in swallowing for 6 months. The esophageal distress was markedly increased on eating solids, but she also experienced some discomfort in taking liquids. Regurgitation occurred immediately after swallowing, but there was no vomiting. Bowels were regular; stools dark in color, showed evidence of blood. There was some loss of weight and a secondary anemia. Roentgenologic gastro-intestinal studies revealed a definite retardation of the barium meal in the lower end of the esophagus. A persistent constriction and a small persistent ulcer niche defect in the constricted area was observed (Fig. 1). The cardia of the stomach is prolapsed through the esophageal opening of the diaphragm. The hernia being of the sliding variety, reduced itself on change of position. The lower esophagus is seen anteriorly and in front of the herniated cardia. The curvatures of the stomach appeared normal and regular in contour; the pylorus filled well; duodenal bulb was regular, did not reveal any signs of ulcer. The remaining intestinal tract showed nothing abnormal.

Roentgen impression: peptic ulcer of lower end of esophagus, with a spastic constriction which retarded the descent of the barium meal. Hernia of the cardia of the stomach through the esophageal hiatus of the sliding variety.

CASE 2.—Mrs. H. C. C., aged 68, complained of having had a hemorrhage 6 weeks ago. She now complained of epigastric distress and discomfort on swallowing, substernal burning and regurgitation, but no vomiting. Stools have been black in color, examination of which showed evidence of blood. There was a marked secondary anemia, with loss of weight. Roentgen examination of the gastro-intestinal tract showed a persistent constriction in the lower esophagus, with a small irregular transient fleck of barium, which was repeatedly observed under the fluoroscope after each swallow of the opaque medium. These findings were observed in two separate examinations (Fig. 2). The cardia of the stomach was herniated through the esophageal hiatus of the diaphragm. The hernia was of the permanent type, which did not slide back into the abdomen on change of position. The contour of the stomach curvatures were regular, the pylorus and duodenal bulb filled well, showed no evidence of ulceration; the colon was dilated and atonic, but emptied normally following an enema.

Roentgen Impression. Peptic ulcer of lower end of esophagus associated with a persistent type of hernia of the cardia of the stomach through the esophageal hiatus of the diaphragm.

Summary. Two cases of peptic ulcer of the esophagus associated with esophageal hiatus hernia are roentgenologically demonstrated. The possibility of peptic ulcer of the esophagus associated with hiatus hernia being a causative factor in the production of anemia should be considered. In a review of the available recent literature, no instance of the coëxistence of peptic ulcer and hernia have been found.

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ACUTE PUERPERAL HYPOPHYSEAL NECROSIS.

WITH REPORT OF A FATAL CASE.

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ACUTE necrosis of the anterior lobe of the pituitary gland in parturient women, although uncommonly encountered, has received some attention recently. Last year Sheehan,[8] of the Glasgow Royal

Maternity Hospital, reported 11 such cases in which death followed delivery within a period of 14 hours to 30 days. A short time after this a similar case came to our attention. Because of the relative infrequence of such reports and the peculiar symptom complex exhibited by the patient we wish to make this brief report.

Mrs. A. C., aged 43, married, white, Gravida I, at term was referred by the family physician to Dr. Eder's service at the Cottage Hospital. A routine history disclosed that she had suffered no serious previous illnesses. She had undergone a tonsillectomy in 1929. Her menstrual periods began at 13, occurred regularly every 28 days, were of the usual duration and amount, and were accompanied by some cramp-like dysmenorrhea. When first seen by her family physician, 6 weeks before term, the patient weighed 131 pounds, the urine showed no albumin and the blood pressure was 159/92. One week later the urine showed a trace of albumin. Two weeks before admission the blood pressure had risen to 162/92 and the urine still showed a trace of albumin. She had lost 1 pound in weight. Her prehospital medication consisted of citrocarbonate and phenobarbital.

On the day of hospital admission her blood pressure was 184/108 and the urinary albumin was 2+. Labor began at 6 A.M., shortly before admission. Examination revealed an apparently full term pregnancy. The pelvic measurements were normal. There was some edema of the ankles and a peculiar brown discoloration of the skin. Labor progressed slowly with irregular shallow contractions. The cervix became fully dilated and effaced after 14 hours of labor. The fetal head was just below the mid-pelvis in O. L. A. position. During the ensuing 2 hours in spite of somewhat stronger contractions no progress was apparent, and in view of the hypertension and albuminuria it was deemed wise to interfere. Under nitrous oxide and ether vapor anesthesia a lateral episiotomy was done and a healthy baby was delivered in O. L. A. position by low midforceps at 10.15 P.M. after something over 16 hours of labor. The soft parts were lacking in elasticity and the episiotomy was extended by a spontaneous laceration along the left vaginal wall. There was considerable bleeding from the laceration and it was immediately repaired. Numerous attempts to express the placenta were unsuccessful. The patient was sent to bed with the placenta retained but with no bleeding. At midnight, 1½ hours later, the patient suddenly became pulseless and blood pressure could not be ascertained. After receiving stimulants and immediate glucose in saline followed by acacia and blood intravenously she recovered rapidly and the placenta was expressed with some difficulty. The blood loss at delivery and placental extraction was not over 700 cc. She received 2 blood transfusions following her placental extraction. For the next 12 hours her condition seemed good and she com-

plained only of headache. Her abdomen then became distended and she began to vomit. No abdominal tenderness or rigidity was noted. Late the second day postpartum her vomiting and abdominal distention were relieved by a Lavine tube and the bowels began to move well. Her general condition, however, was not good. Her pulse remained about 120 and the temperature rose from 100 the first day postpartum to 103 the third and fourth. She was restless and complained of headache, became mentally confused and on one occasion got out of bed. On the third day postpartum, in spite of intravenous solution and ephedrine, the systolic pressure stayed below 90. Readings on the fourth and last day postpartum were 60/30, 90/65, 75/30, 50/20, 55/25, 90/48. She became drowsy and cyanotic and died 93 hours after delivery. Her fluid intake was above 4000 cc. per day and the urinary output was 1700 cc., 6120 cc., 5780 cc. and 1400 cc. on the successive days after delivery. The blood picture on the last day was R.B.C., 4,100,000; Hb., 82%; W.B.C., 15,000.

Postmortem Examination (½ hour after death). External examination: The body is that of a well-developed middle-aged white woman. The skin has a faint, yellowish-brown color apparent equally on all surfaces. The breasts are full and nipples are slightly excoriated. The abdomen shows slight diastasis of the lower rectus muscles. There is scant subcutaneous fat and the tissue hydration is good. Incision: Y-type, serous cavities negative. Heart: 290 gm., negative. Lungs: Right, 215; left, 175 gm., negative. Gastro-intestinal tract: Shows the colon distended moderately with fluid. Liver: 2100 gm. Scattered beneath a thin capsule are irregular yellowish mottled areas. Section shows these to be scattered at random through the liver substance. The lobular units are visible. The cut surface is dark and bloody. Spleen: 250 gm., firm and dark. Kidneys: Right, 155 gm.; left, 140 gm., both similar. The capsule strips with ease. The cortex and medulla are of good thickness. The renal pelves are slightly hemorrhagic. The ureters are slightly dilated. Uterus, tubes and ovaries: The tubes are injected and edematous and the ovaries small and soft. The uterus measures 25 by 15 by 10 cm. Its endometrium is shaggy and is covered by a layer of clotted blood 1 cm. thick. Smear of the endometrium and tubal mucosa shows Gram-negative and Gram-positive diplococci. Pancreas: 100 gm. normal. Adrenals: Negative. Lymph nodes and skeleton: Negative. Brain: 1150 gm. negative. Pituitary: Weight, 1 gm. It is softened and has a yellow color. (Necrosis at this time was not suspected.) Cerebral vessels are soft and dilated.

Bacteriology: Blood culture negative.

Microscopic. Heart, lung, stomach, spleen, kidneys, negative. Liver: Dilatation of the central venules with blood is noted but the

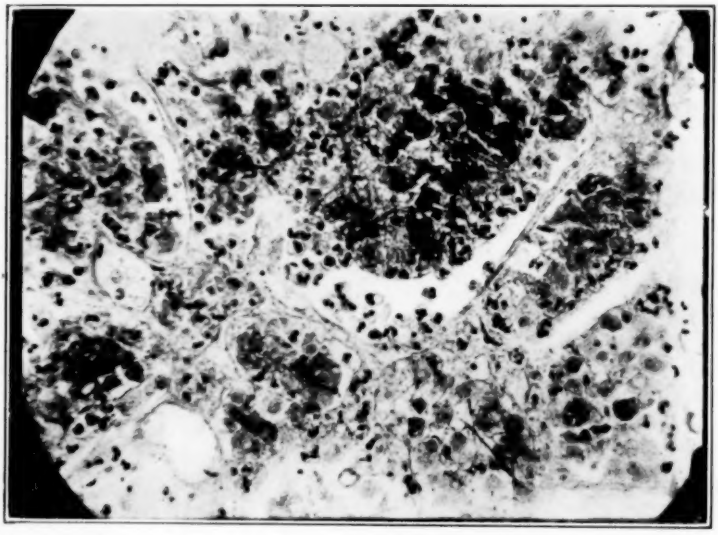

FIG. 1.—The cellular detail is lost. There is a focus of coagulation necrosis in the center. Polymorphonuclears infiltrate the necrotic cells. Fibrin is deposited at the lower edge of the section. (× 400—Mallory's phosphotungstic acid hematoxylin.)

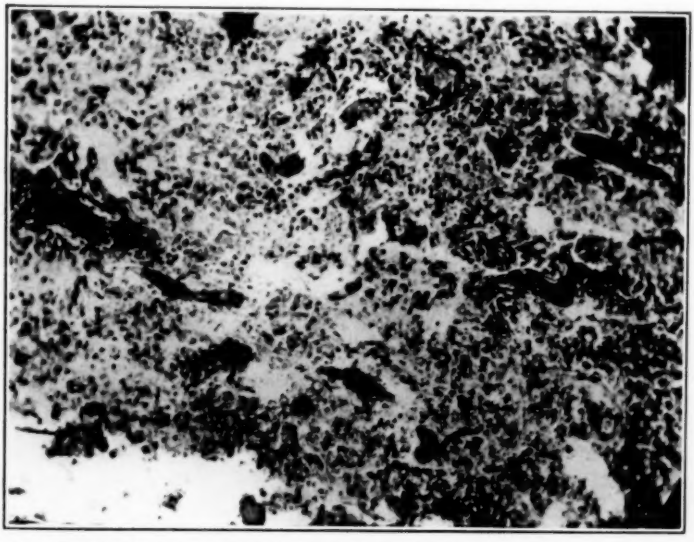

FIG. 2.—The alveolar structure of the hypophysis is lost. The gland cells stain poorly. Hyaline and fibrin thrombi fill the sinusoids. (× 180 H. and E.)

liver cells remain intact. Uterus: Many of the distended cavernous vessels of the endometrium are filled with red thrombi. The fibrin coating on the endometrial surface is infiltrated with neutrophils. The muscle fibers are hypertrophied and indistinct. Ovary and pancreas: Negative. Adrenal: The cortex is of good thickness. The outer cortical cells are vacuolated and appear intact throughout. The medulla is thin but is otherwise negative. The adrenal does not fall into any of the exhaustion types as outlined by Zwemer.[10] Section of voluntary muscle is negative. Brain: Sections of the brain stem, medulla and cerebrum show moderate perivascular edema only. Pituitary: In the pars anterior all cells stain poorly and are blurred. Only occasional nuclei can be differentiated from their homogeneous amorphous eosinophilic cytoplasm. Some cells are darker than others, suggesting that they are basophils, but necrobiosis has progressed to the stage where cell identification is hazardous. Polymorphonuclear neutrophils occupy many cavernous channels and invade areas of frank gland cell necrosis (Fig. 1). A few minute foci of apparently intact cells remain. Numerous hyaline and fibrin thrombi are noted in the vascular sinusoids (Fig. 2). The endothelium of these channels does not appear viable at points of thrombosis. The appearance of the gland is one of infarction. Gram stain fails to show any bacteria in the section. Only one piece of the pituitary was cut. The remainder of the gland was assayed for adrenotropic and gonadotropic hormones by Dr. Bischoff. Neither of these could be demonstrated. The absence of gonadotropic hormone is very significant inasmuch as small amounts of this have been found to be easily assayable. The microscopic sections do not include the posterior pituitary.

Discussion. In his excellent review (1937)* of some 60 cases of acute anterior pituitary necrosis collected from the literature, Sheehan[8] points out that the greatest number with massive involvement occurred postpartum. A similar association was noted by Simmonds[9] in the condition of chronic hypophyseal insufficiency which bears his name. The mechanism of the necroses occurring at or just after delivery is in some question. The theory of embolism advanced by many previous authors cannot explain the majority of cases, particularly those without endocardial disease or embolic residua elsewhere. The concept of thrombosis of the vascular channels in the gland due to both local and general conditions is on firmer ground. Changes in the blood at the puerperium such as increased fibrinogen content and platelets favor such a hypothesis. Postpartum hemorrhage with retained placenta should augment the coagulability of the blood. The prompt puerperal involution of the pituitary as detailed by Erdheim and Stumme[4] would

* In view of the availability of this recent and excellent review it has not been deemed desirable to discuss the literature on this subject.

seem to favor vascular thrombosis locally, as well as the effect of ischemia from shock and syncope occurring at delivery on the vascular endothelium of the gland. Puerperal infection has been noted prior to the pituitary change in only a portion of the cases of acute necrosis reported, so that this factor does not seem essential to the incidence of thrombosis.

Prominent signs and symptoms which appeared during our patient's postpartum course were nausea and vomiting, headache and hypotension. Ileus could explain the first symptoms. Recourse to the pituitary to explain the headache and hypotension has some appeal. Local hypophyseal inflammation could account for the headache. The extreme hypotension occurring on the fourth day after her delivery, when the erythrocytes numbered over 4 million per mm. and when no sign of hemorrhage was present, certainly finds difficulty in explanation from the standpoint of shock, especially since the amount of fluid (glucose, saline and blood) administered intravenously was more than sufficient to maintain blood volume. A large urinary output would not be expected if the condition were due to shock. The assumption of a pituitary origin of her hypotension seems preferable to that of shock.

A certain amount of clinical evidence is at hand concerning the association between pituitary insufficiency and hypotension. Cushing[3b] has pointed out that pressure on the hypophyseal stalk from tumor with resulting partial anterior lobe necrosis was associated frequently with unmistakable degrees of hypotension, in one case 85/50, in another 60/50. Houssay[5] quotes similar cases associated with tumors of the hypophysis. He recognizes also the possibility of hypotension resulting from posterior lobe hypofunction but states that in the rat, dog and human it probably reflects a deficiency of the anterior lobe. In 1932, Calder[1] discussing Simmonds' disease raised the question of whether hypotension and asthenia were incident upon pituitary insufficiency directly or secondarily upon adrenal insufficiency. Assuming the hypotension to be glandular in our case, the absence of adrenal change and the presence of morphologic and biologic pituitary insufficiency leaves us little choice but to implicate the pituitary directly.

The question may well be raised whether the pituitary necrosis was a coincidental or major factor in this woman's death. It seems unlikely that a sapremia from uterine and tubal infection of 3 days' duration was the main factor in her demise. The issue becomes one of whether the human can tolerate the sudden absence of pituitary function. It was shown after years of debate that the sudden and complete removal of the pituitary in laboratory animals did not cause death promptly in many of them. It is also known that almost complete destruction of the anterior lobe may be a chance finding at autopsy without clinical disturbance having been detected

during life (Krumbhaar[6]). Cushing's and Crowe's (*et al.*)[2,3a] early experimental work indicated, however, that many of their hypophysectomized dogs developed loss of interest, irritability, anorexia, muscle twitching, lethargy, coma and death. Mahoney[7a,b,c] noting the similarity between this syndrome and hypoglycemia showed that in both the dog and monkey these frequently fatal hypoglycemic accidents could be avoided by large amounts of glucose. We do not know whether our patient displayed this condition. She took small amounts of liquid nourishment by mouth for 2 days after delivery and received about 305 gm. of glucose intravenously during her puerperal course. The lack of other postmortem findings sufficient to explain this patient's rapidly fatal puerperal course, however, inclines us to assign major significance to the acute hypophyseal insufficiency known to be present.

Summary. 1. A case of acute thrombosis and necrosis of the anterior pituitary, terminating fatally during the puerperium, is reported.

2. The endocrine deficiency resulting therefrom is shown and its possible effects briefly discussed.

3. It is suggested that this may be a more common puerperal complication than is usually recognized, and that should the puerperal course of a patient progress unfavorably without obvious cause, blood sugar studies, active glucose therapy and anterior pituitary extracts might be in order.

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THE PROLONGATION BY ZINC SALTS OF A WATER BALANCE REACTION OF POSTERIOR HYPOPHYSEAL EXTRACT.*

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Interest in the effect of salts of zinc upon the activity of hormones has arisen from two lines of approach. The first of these

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was and is concerned with the action of various activating substances, by themselves inactive, upon hypophyseal, gonadotropic substances. In 1934, Maxwell[6] found that zinc sulphate increased the gonadotropic function of pituitary extracts and advanced the idea that this was due to a decrease in the rate of absorption of the injected extract. Fevold, Hisaw and Greep[4] found that zinc sulphate added to extracts containing the follicle stimulating hormone (F.S.H.) or follicle stimulating hormone (F.S.H.) plus luteinizing hormone (L.H.) produced ovaries in immature or hypophysectomized rats which weighed 2 to 3 times as much as in animals receiving the extract without the zinc. Similar results were obtained by Saunders and Cole.[11]

The second line of approach came especially from the investigations of Scott and Fisher,[12] who noted that insulin containing 0.1% of zinc had a more prolonged hypoglycemic effect upon rabbits than insulin alone. These results were confirmed in patients with diabetes mellitus by Rabinowitch and his associates.[5,7–9]

Dodds, Noble, Rinderknecht and Williams[3] visualized from the above work the possibility that zinc salts may have a general prolonging effect upon the action of other hormones. They state that Rosenthal and Kamlet[10] found that zinc prolonged the action of diphtheria toxin; but the paper to which they refer does not make this statement nor, indeed, is it concerned at all with zinc. Dodds *et al.*[3] conclude that zinc prolongs the gastric secretion of hydrochloric acid produced by histamine in cats with gastric fistulæ but their Figure 2 presented in exemplification does not indicate clearly the experimental basis of this conclusion. They further demonstrated that the addition of zinc acetate considerably prolongs the inhibition of water diuresis in rats by injection of extract of the posterior hypophysis.

The present investigation was designed to investigate the effect of salts of zinc added to posterior hypophyseal extracts and injected into frogs. Under such circumstances, posterior pituitary extracts themselves produce an uptake of water amounting to 15 to 25% of the weight of the animal in 3 to 4 hours at room temperature and this reaction is not identical to the inhibition of water diuresis in mammals.[1,2] Zinc was found to prolong the retention of water so taken up and experiments were devised to elucidate the mechanism involved.

Method. The general procedure used was described by Boyd and Brown.[1] Leopard frogs (Rana pipiens) were placed in water in individual beakers, injected with 0.5 international units of pituitrin surgical* per 10 gm. body weight containing various amounts of zinc. The animals were weighed to the nearest 0.1 gm. before and at intervals of 1 hour after injection. From 6 to 24 frogs were used in each experiment with similar numbers as controls, (*a*) without pituitrin and (*b*) without zinc. The

* Supplied in generous quantities by Dr. E. A. Sharp, of Parke, Davis & Co.

experiments were performed in an open laboratory and in view of the finding of Boyd and Whyte[2] that insensible air currents in an open, ventilated room may cause appreciable evaporation of water from exposed skin of frogs in beakers, experiments were done to find means of preventing this. It was finally noted that if the frogs were almost completely immersed in water (200 cc. in a 400 cc. beaker) the uptake of water was practically the same whether the experiment was performed in a dark, unventilated room or in an open laboratory or whether or not beakers were covered with glass sheets instead of wire covers, which were criteria used by Boyd and Whyte[2] to study the dehydrating effect of insensible air currents. It is necessary to emphasize this detail in technique because, as shown by Boyd and Whyte,[2] failure to eliminate or take into consideration evaporation from such air currents is the probable explanation of discrepancies in the results of reports in the literature.

The Effect of Zinc Acetate on Intramuscular Injections of Pituitrin. Solutions of zinc acetate were prepared containing different amounts of zinc calculated as zinc and not as zinc acetate. The solutions were mixed in equal parts with fresh surgical pituitrin and 0.05 cc. of the resultant mixture were injected intramuscularly into frogs for each 10 gm. of body weight, this amount containing 0.5 international units of pituitrin. Other groups of frogs received the same amount of pituitrin combined with an equal amount of distilled water and a still further group received corresponding amounts of zinc with distilled water substituted for the pituitrin.

The results obtained in a number of typical experiments are listed in Table 1. In this work, in contrast to previous reports

TABLE 1.—THE EFFECT, ON WATER UPTAKE, OF ZINC (AS ZINC ACETATE) ADDED TO PITUITRIN AND INJECTED INTRAMUSCULARLY INTO FROGS.

Pituitrin per 10 gm. body weight, units.	Zinc added to pituitrin, %.	Number of animals.	Mean maximal uptake of water, %.	Time after injection of maximal uptake, hrs.	Duration of water retention, hrs.
		Pituitrin without zinc.			
0.5	None	12	21.4	2.0	6.5
0.5	None	12	22.1	2.5	6.5
0.5	None	6	20.3	3.0	7.0
0.5	None	6	20.4	2.5	7.0
0.5	None	6	17.8	3.0	7.5
0.5	None	6	20.8	2.5	8.0
0.5	None	6	19.3	2.5	8.0
0.5	None	12	22.9	2.5	8.0
0.5	None	12	23.4	3.0	8.5
		Pituitrin with zinc.			
0.5	0.01	6	17.8	2.0	7.0
0.5	0.02	6	17.8	2.0	7.0
0.5	0.08	6	17.2	3.5	9.0
0.5	0.1	6	18.8	3.0	9.5
0.5	0.1	12	24.8	3.0	10.0
0.5	0.1	12	21.7	3.0	10.0
0.5	0.4	8	18.1	3.0	13.0
0.5	0.6	6	23.2	2.0	15.0
		Zinc without pituitrin.			
None	0.08	6	1.1	3.0	5.0
None	0.1	6	2.2	1.5	5.0
None	0.1	24	2.2	2.5	6.0
None	0.2	6	6.2	1.5	9+
None	0.4	6	5.3	1.5	10+

from this laboratory,[1,2] interest centered chiefly on the length of time frogs retained water taken up as a result of injecting pituitrin. In preliminary trials, the time required for the weight of the frog to return to exactly the initial weight was found to be extremely variable. In fact, it was found that the weight of normal, uninjected frogs in water may vary from hour to hour by as much as ±3%. The impression was gained that the normal equilibrium between the water inside and outside the frog may be in a constant state of flux and vary within these limits. Hence it was decided to accept as the end-point of the effect of pituitrin the time when the weight of the frog had decreased to within 3% of the initial and such values are included in the extreme right-hand column of Table 1 (except figures for the group "Zinc Without Pituitrin" where duration means the hours required to come back to the initial weight ±0.05%).

When pituitrin alone was injected, the end-point of the reaction occurred in from 6.5 to 8.5 hours in the different groups, on the average. Zinc added to a concentration of less than 0.08% had no effect upon the duration of water retention but concentrations of zinc above 0.08% definitely prolonged the retention. The optimum concentration of zinc was found to be 0.1%, and this amount prolonged water retention by an average of one-third the normal time. Zinc had no effect upon the height of the reaction, *i. e.*, it did not affect the maximal uptake of water, although it may have slightly deferred the time at which the peak occurred.

Concentration of zinc greater than 0.1% caused an even greater prolongation of the reaction, but such doses became increasingly more toxic. This was evidenced by an uptake of water by those frogs receiving zinc alone, an uptake which was in excess of the normal variation in weight of 3%. Such water was retained for a long time, many animals being found to have held it for over 24 hours. With concentrations of zinc less than 0.2% there was no appreciable effect upon the weight of the animal from the zinc itself. When a concentration of 0.4% zinc was used (20 mg. of zinc per kilo or about one-fifth of the lethal dose per kilo by mouth in man), many animals became and remained water-logged and sluggish and the average mortality was 33%. The mortality rate increased until, when 2% of zinc was used, all animals died.

It may be concluded from these experiments that the addition of 0.1% of zinc to pituitrin prolongs the retention of water taken up by frogs when pituitrin is injected intramuscularly. Lesser concentrations of zinc become progressively less active and greater concentrations progressively more toxic.

Is the Effect Due to Zinc or to the Negative Ion? Studies under this heading were made of the comparative effect of several salts of zinc and demonstrated that all water-soluble salts which were examined were equally efficacious providing that the negative radicle

was not toxic in the dose used. The zinc salts studied were the acetate, chloride, nitrate, sulphate, bromide, iodide, permanganate and sulphocarbolate (phenolsulphonate), all of which were added in equal parts to pituitrin surgical to produce a final mixture containing 0.1% of zinc as zinc. All salts prolonged the water retention over pituitrin alone by 20 to 60%. The first 4 were non-toxic as far as could be seen from no change in body weight or physical activity of the animals, but control animals receiving zinc alone showed an appreciable increase in weight with all of the last 4 salts named which were hence considered toxic in this dose.

The Site of Injection. Dodds *et al.*[3] state that intravenously injected zinc mixtures do not exhibit zinc-prolonging action and conclude that zinc acts by retarding absorption of the hormone when injected into tissues. This idea was examined by injecting zinc-pituitrin mixtures (*a*) intramuscularly, (*b*) subcutaneously and (*c*) into the dorsal lymph sac. From a total of 18 experiments, each with 6 to 12 frogs given the mixture, an equal number receiving pituitrin alone and another equal number receiving zinc alone, it was found that zinc was most effective when given intramuscularly, less so given subcutaneously and practically without effect when injected into the dorsal lymph sac. These results lend support to the conception that zinc salts act in some manner upon tissues at the site of injection, probably by retarding absorption of the hormone.

Is There a Reaction Between Zinc and Pituitrin? The alternative explanation of the effect of zinc is that it may combine chemically or physically with the water balance principle in pituitrin forming a substance which is either more slowly absorbed or has a more prolonged action. This suggestion was studied in four ways:

1. If the pituitary principle combines with zinc and if this hypothetical reaction is a slow one, then allowing zinc and pituitrin mixtures to stand for varying periods should produce more of the hypothetical zinc-pituitrin compound and hence injections of such mixtures should give increasingly more effective prolongations. Such was not the case. When pituitrin was combined with 0.1% of zinc (zinc acetate used in this and subsequent work) and immediately injected, the effect was just as good as when the zinc pituitrin mixture was allowed to stand in the icebox for periods up to 21 days.

2. A chemical reaction should be augmented by heat, so mixtures of pituitrin and zinc were made and boiled for periods up to 15 minutes, adding regularly hot distilled water to keep the mixture to its original volume. Boiling for this period was found to have no effect upon the reaction of pituitrin itself in frogs, nor did it increase the effectiveness of the zinc-pituitrin mixtures.

3. A proposed chemical reaction between zinc and pituitrin may have an optimum pH. The pH of mixtures of zinc and pituitrin was altered by adding varying amounts of Sörenson's phosphate

mixtures, sodium hydroxide, hydrochloric acid, nitric acid and glacial acetic acid and mixtures were injected intramuscularly with a pH from 2.6, which was below the normal pH of zinc acetate and pituitrin (4.2), to as high as 7.6, at and above which zinc tended to precipitate out of solution. Zinc prolonged the action of pituitrin the same amount at all hydrogen-ion concentrations. There does not appear to be any need to neutralize zinc-pituitrin mixtures as described by Dodds *et al.*[3]

4. If zinc and the pituitary factor combine chemically, such a reaction might be lessened by diluting the medium in which it is proposed that the reaction occurs. Mixtures of zinc acetate (0.1%) and pituitrin were diluted 1, 2 and 3 times with equal parts of distilled water. Such diluted mixtures gave results identical to the undiluted mixture.

These results provide no evidence that zinc combines in any way with the pituitary principle to produce a new substance which has a more prolonged action on water retention in frogs.

Does Zinc Combine With Tissue Protein to Delay Absorption of Pituitrin? The conception advanced by Maxwell[6] and re-stated by Dodds *et al.*[3] that zinc prolongs hormonal reactions by retarding tissue absorption of the active principle at the site of injection was investigated in two further ways in addition to the experiments on the site of injection described above.

1. It is well known that zinc precipitates protein and hence it appeared that adding a solution of protein to zinc-pituitrin mixtures might enhance the effect when injected into the dorsal lymph sac, at which site zinc ordinarily has little effect. Such combinations were made of equal parts of the zinc-pituitrin mixture and of blood plasma of guinea-pigs with controls receiving plasma alone, pituitrin alone and zinc plus pituitrin. The results were not particularly striking but when injected into the dorsal lymph sac, the mixture of plasma-zinc-pituitrin prolonged the retention of water for an interval 15% longer than zinc-pituitrin or pituitrin alone, both of which again gave identical results. The plasma had no appreciable effect by itself in the amount (0.05 cc.) used nor did it alter the effect of subcutaneously or intramuscularly injected pituitrin.

2. If zinc is injected intramuscularly alone, it should immediately combine with tissue protein and if pituitrin be subsequently injected into the same site it should have: (*a*) a typical prolonging effect if zinc binds pituitrin to muscle, or (*b*) no prolonging effect if pituitrin must first combine with zinc. A needle was injected into frog muscle and zinc injected; 1 minute later pituitrin was injected with a second syringe into the same site through the same needle which had meanwhile been left *in situ*. A typical prolonged water retention was obtained.

These experiments support the view that zinc prolongs the pituit-

rin effect in frogs by binding pituitrin at the site of injection in tissue and prolonging its absorption rather than by combining with pituitrin to form a new substance.

Summary. The addition of 0.1% of zinc, in the form of a suitable salt, to pituitrin injected into frogs prolongs the retention of water taken up by them. Lower concentrations of zinc are progressively less active and greater concentrations are progressively more toxic. All water-soluble salts of zinc investigated, which were not toxic at this dose, had the same effect. Evidence is presented favoring the view that the effect of zinc is upon the tissues at the site of injection rather than by the formation of a new compound between zinc and the active principle in pituitrin.

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THE CHOICE OF TECHNIQUE FOR THE SEDIMENTATION TEST.

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In the 20 years since the red cell sedimentation test was introduced by Fahraeus, a voluminous literature has appeared and considerable confusion has arisen due to the multiplicity of methods by which this originally simple test has been carried out (see Pinner, Knowlton and Kelly[9]). Many of the proposed newer methods aim only to simplify the originally very simple and practical technique of Westergren, which is favored by Fahraeus, but it is doubtful if much can be achieved in this direction. On the other hand, some authors believe that the simpler sedimentation procedures, of which the Westergren method is typical, have inherent defects which can be eliminated by modifications in the technique, and they have proposed methods which aim to overcome these defects and thus to yield more accurate results. Usually it has been on theoretical

grounds that these modifications have been advanced. The aim of this paper is to examine the validity of these claims, and to determine whether the simpler sedimentation methods are really defective, and lead in many cases to inaccurate results.

The chief criticisms[11,12] made against the Westergren and similar methods are as follows:

1. Dry citrate or oxalate lowers the sedimentation rate, while heparin does not influence the sedimentation rate.

2. Citrate or oxalate solution has a still more pronounced effect in lowering the sedimentation rate.

3. Due to cell volume variation in different blood samples, the citrate concentration in the resultant plasma must vary, and this will influence the sedimentation rate.

4. It is the maximum uniform sinking velocity of the red cells, and not the 1-hour reading, which expresses the essential result of the test. Related to this is the claim that graphic methods of presenting the results of the test, for example the Cutler technique,[3] give valuable information which is lost when only the 1-hour reading is taken.

5. The Westergren method does not correct the observed sedimentation rate for the effect of red cell volume or cell count.

Before examining these claims, it is well to keep in mind that all of the numerical scales, in terms of which the sedimentation rate has been recorded, are arbitrary ones. If two methods of performing the sedimentation test are equally satisfactory and reliable, there should exist a consistent relation between the results obtained by these two methods, though this relation may take the form of a curve, and not of a straight line, when plotted as a graph. But either scale of results would be equally satisfactory in clinical practice. This is important since it will be pointed out that the statement "dilution with citrate alters the sedimentation rate" may imply only that a *definite and consistent* change is introduced into the numerical results of the test, *e. g.*, the number of millimeters sedimentation in 1 hour. Where this is the case the sedimentation rate results obtained on citrated blood are as accurate and reliable as results obtained by some other method, and the objection to the use of citrate is unfounded.

1. *Effect of Dry Citrate or Oxalate Upon the Sedimentation Rate.* It is generally accepted that small amounts of heparin can be used as anticoagulant without affecting the sedimentation rate. A comparison of the 1-hour sedimentation rates, using heparin and dry oxalate as anticoagulants, was made by Wintrobe and Landsberg,[15] who found that the use of oxalate did not retard the sedimentation rate.

When heparin is used as anticoagulant, there is usually a longer delay before a uniform sedimentation rate is reached, while with citrated or oxalated blood, sedimentation commences more promptly.

Hence a fair comparison of the relative effects of heparin, citrate and oxalate upon the sedimentation rate can best be made by measuring the "uniform sinking velocity," *i. e.*, the velocity of sedimentation during that intermediate phase when it is assumed that neither the preliminary delay for aggregation of the red cells, nor the final delay due to packing of the cells in the lower part of the tube, are operative.*

The method employed to make this comparison was as follows: to duplicate 2 cc. portions of blood from each of 27 persons was added 1 drop of heparin solution (150 mg. to 1 cc. water) or 1 drop of 35% sodium citrate solution; the drops of heparin or citrate solution were of approximately the same size, about 0.022 cc. After cooling to room temperature and well mixing, the samples were transferred by capillary pipettes to Wintrobe type sedimentation tubes, giving blood columns 100 mm. high and 4 mm. diameter. Readings, estimated to the nearest 0.1 mm. were taken at 2-minute intervals and the uniform sinking velocity was measured from the graph of each sedimentation.

The data obtained are plotted in Figure 1, and show that no significant change in sedimentation rate is produced by using citrate in place of heparin. The correlation coefficient is 0.97 ± 0.01.

The contention that certain electrolytes under certain conditions can influence the suspension stability of blood is beyond question. But with the specific electrolytes in question, *i. e.*, dry oxalate or citrate, and in the concentrations actually employed, the evidence quoted above indicates that they produce no significant effect upon the sedimentation rate.

2. *Effect of Isotonic Oxalate or Citrate Solution Upon the Sedimentation Rate.* If an isotonic oxalate or citrate solution is employed as anticoagulant, instead of the dry salt, another factor is introduced; the blood plasma is diluted, and this lowers the concentration of those substances which increase the sedimentation rate. Hence this factor tends to lower the sedimentation rate. On the other hand, dilution with oxalate or citrate solution tends to accelerate the sedimentation rate by reducing both the percentage of red cells, and the viscosity and specific gravity of the plasma. The sum total of these effects, as found by experiment, is given in Figure 2, which is taken from Figure 8 of Westergren's article.[13b] This figure compares the 1-hour readings, in the Westergren sedimentation tube, of undiluted citrated blood (*i. e.*, blood drawn into a syringe slightly moist

* Most authors interpret the period of uniform sedimentation to indicate that the red cell aggregates reach a maximum and constant size, and then settle with a velocity which is an expression of Stokes' law, provided allowance is made for the proximity of other aggregates. This view needs to be qualified. As sedimentation proceeds, the red cell aggregates in the lower part of the tube are brought closer together, and this alone retards sedimentation long before complete packing of the cells occur, for, as Lundgren[8] puts it, the aggregates in the upper part of the tube tend to lean upon those below. Lundgren finds that the red cell aggregates increase in size throughout the test, and the period of uniform sinking velocity is merely that phase during which any increase in velocity due to increasing size of aggregates is offset by the retarding effect due to their increasing proximity.

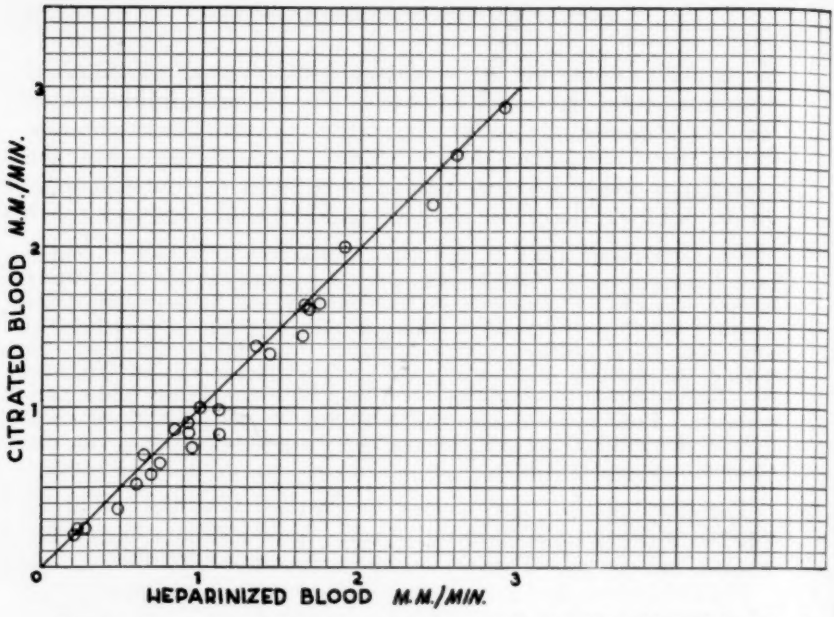

FIG. 1.—Comparison of the uniform sinking velocities of undiluted heparinized blood and undiluted citrated blood.

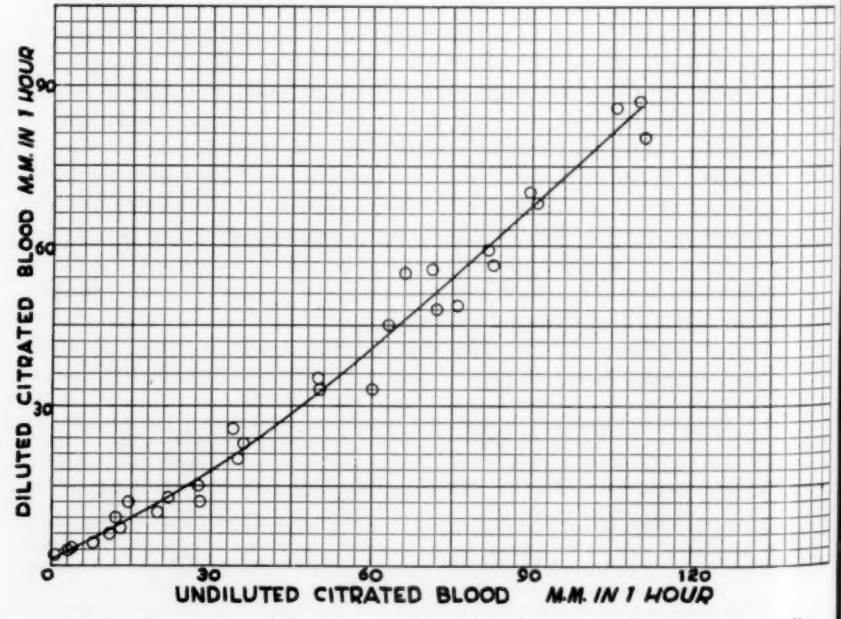

FIG. 2.—Comparison of the 1-hour sedimentation distance, in the Westergren sedimentation tube, of diluted and undiluted citrated blood. (After Westergren.)

with 30% citrate) with diluted citrated blood (4 vols. blood to 1 vol. 3.8% citrate). Allowing for the curvilinear relationship, the correlation coefficient is 0.95 ± 0.014. In Figure 3 are given the data obtained here of the relative sinking velocities, mm. per minute in the Wintrobe sedimentation tubes, of undiluted heparinized blood and of diluted citrated blood (85 vols. blood to 15 vols. of 3.8% citrate). This graph shows a correlation coefficient of 0.96 ± 0.01. In each case a consistent relation is found to exist for all types of blood, normal or pathologic, between the sedimentation rates on undiluted blood and on blood containing 15 or 20% of citrate solution. The statement that "dilution with citrate affects the sedimentation

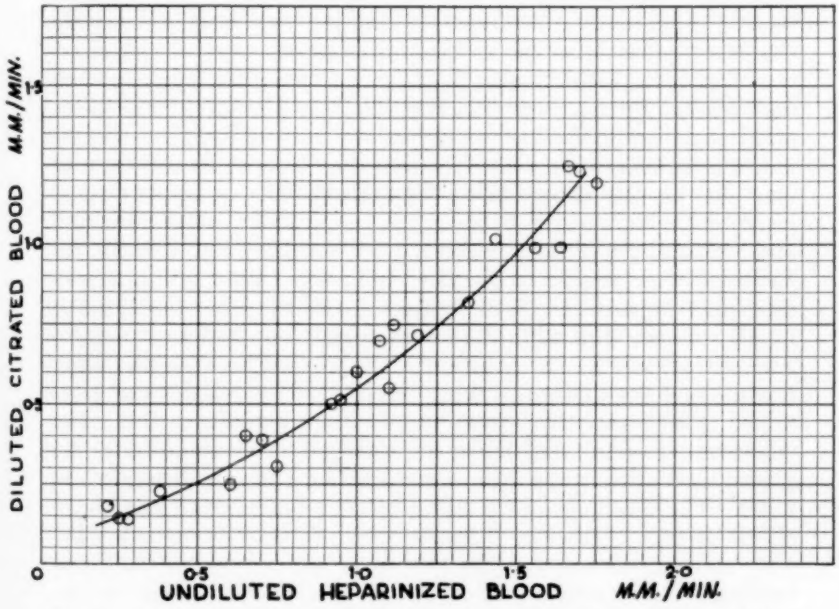

FIG. 3.—Comparison of the uniform sinking velocities of undiluted heparinized blood and diluted citrated blood.

rate" is misleading unless it is recognized that while the numerical results of the sedimentation test are modified, this change in the scale of results is a consistent one, and hence gives a satisfactory scale in terms of which to denote sedimentation rates.

3. *Effect of Varying Citrate Concentration in the Plasma.* It has repeatedly been pointed out that when blood and citrate solution are mixed in constant proportions, the citrate concentration in the resultant plasma is not constant, but varies according to the percentage red cell volume of the blood. Any changes of the sedimentation rate as a result of this are probably due to differing degrees

of dilution of the plasma, rather than to citrate concentration *per se*. However that may be, this criticism of the use of citrate solution as anticoagulant does not apply to the results of the Gram[5] or Hambleton-Christianson[6] methods, in which the results are simultaneously corrected for this factor and for the effect of cell volume. The results obtained by other methods which employ citrate as anticoagulant, *e. g.*, those of Westergren, Cutler and Linzemeier, should theoretically be influenced by the varying citrate concentration in the plasma. Westergren[13b] investigated this point, but his data show that regardless of whether blood is of high or low cell volume, the sample after dilution with citrate solution gives a sedimentation rate bearing a consistent ratio to that of the undiluted blood. Apparently this factor of dilution produces no clinically significant effect upon the sedimentation rate.

4. *Use of the Single 1-hour Reading in Place of the Uniform Sinking Velocity.* From a theoretical standpoint, as Lundgren,[8] Fahraeus,[4] and Rourke and Ernstene[11] point out, it is preferable to measure the uniform sedimentation velocity rather than to take the 1-hour reading. In the case of undiluted heparinized blood it seems that no consistent relation exists between the 1-hour sedimentation distance and the uniform sinking velocity; due to this fact, Rourke and Ernstene were unable to prepare, from the 1-hour sedimentation rates upon heparinized blood, uniform curves to correct for the effect of cell volume. But with blood containing 15 or 20% by volume of 3.8% citrate solution, a consistent relation exists between the 1-hour reading and the uniform sinking velocity. This relation, as determined in 50 consecutive blood samples from patients in this tuberculosis sanatorium, using blood containing 15% citrate solution, and placed in the Wintrobe type sedimentation tube, is shown in Figure 4. These samples were taken without reference to age, sex, or extent or type of disease. Samples which settle 50 mm. or less in 1 hour show an almost straight line relationship between the 1-hour reading and the uniform sinking velocity, and over this range the correlation coefficient is 0.98 ± 0.01. This type of tube has a blood column only half as long as that in the Westergren tube, and due to packing at the bottom of the tube, variations in cell volume influence the 1-hour reading when this is greater than 50 mm.; this prevents the existence of a consistent relationship above this figure.

A similar comparison of the 1-hour reading to the uniform sinking velocity was made by the Westergren technique, using blood samples from 39 patients. The results are given in Figure 5, and these also show a good correlation, the coefficient being 0.97 ± 0.01.

Westergren[13b] states that in some cases of jaundice associated with some other disease which gives a high sedimentation rate, there is an unusually long aggregation period before uniform sedimentation commences; Westergren, Theorell and Widström[14] state that pos-

sibly abnormal lipoid factors in the blood may lead to rare sedimentation curves of this type. However, no such instance has been encountered in the 100 patients covered in this work.

When blood samples containing 15 to 20% by volume of isotonic citrate solution are placed in sedimentation tubes giving blood columns of 100 or 200 mm. length, the data given in Figures 4 and 5 indicate that the 1-hour reading provides the significant information concerning the sedimentation rate. To measure the uniform sinking velocity requires considerable time from the operator, and gives essentially the same result, expressed in a different numerical scale.

The Cutler Technique. This method has come into rather wide use, but the data presented above do not justify the claims made for it. A short sedimentation tube (50 mm. blood column) is employed in the Cutler technique;[3] readings are taken every 5 minutes or so, and plotted on a graph. Results are then expressed in 3 terms: *a*, the 1-hour sedimentation; *b*, the "sedimentation time," *i. e.*, the time until packing of the cells at the lower part of the tube reduces the sedimentation rate to 1 mm. in 5 minutes; and, *c*, the visual appearance of the graph.

The objection to this method is that results are expressed in a confusing manner. The true characteristic of the sedimentation test is the uniform maximum settling velocity.[8] As pointed out and illustrated in Figures 4 and 5, with citrated blood in tubes of 100 to 200 mm. length, a single 1-hour reading gives essentially the same data as the uniform sinking velocity. But in the short Cutler tube, the 1-hour reading is markedly influenced by the packing of the cells at the bottom of the tube, if the blood samples have a moderately fast settling rate. The defect of the Cutler technique is that the tubes employed are too short. If rapidly settling blood is placed in these short tubes, then as Cutler states, the 1-hour reading is perhaps the least important observation that can be made. But this remark is not true for the longer Westergren tube, with which the 1-hour reading gives the clinically significant data. Except for the slowly settling bloods, the end result of the Cutler test cannot be given by a single figure, but is some function of the three factors recorded—sedimentation distance, sedimentation time, and visual appearance of the graph. Thus the interpretation and comparison of results from the Cutler technique is more difficult than is the case with the clean-cut results of the Westergren method.

5. *Correction for the Effects of Cell Volume, Cell Count or Hemoglobin Content.* In our present state of knowledge, there is no justification for correcting the observed sedimentation rate for the effects of cell volume, cell count or hemoglobin content. All such methods of correction are based on *in vitro* findings, when the ratio of cells to plasma is artificially changed. In practice other factors are involved[4,13b]

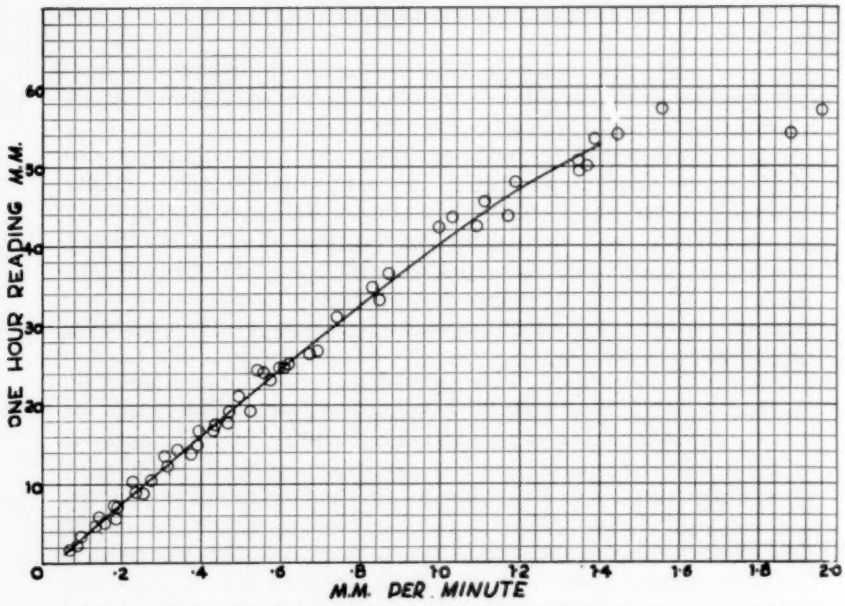

FIG. 4.—Comparison of the uniform sinking velocity to the 1-hour sedimentation distance of citrated blood in the Wintrobe sedimentation tube; 100 x 4 mm. blood column.

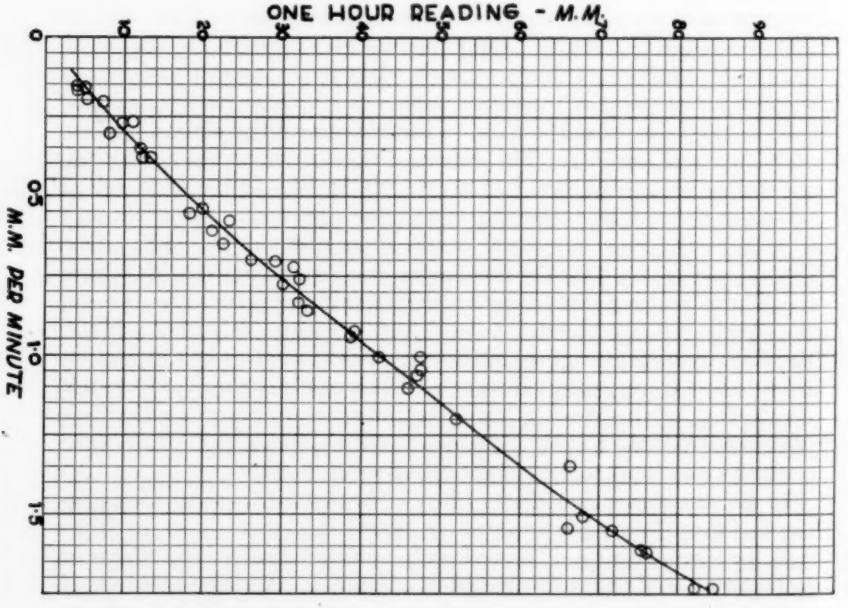

FIG. 5.—Comparison of the uniform sinking velocity to the 1-hour sedimentation distance of citrated blood in the Westergren sedimentation tube; 200 x 2.5 mm. blood column.

and there is evidence that when corrections are made to the sedimentation rate, greater errors are introduced than those which are avoided.[7,13b,14] The data obtained at this sanatorium[2] from a comparison of corrected and uncorrected rates to the clinical condition of the patients support this view; in fact, correcting the sedimentation rate on the basis of the *in vitro* effects of cell volume, and so on, irrespective of the technique employed, at times leads to results which are clinically absurd.

A Comparison of the Results of the Rourke-Ernstene Technique[11] *With Those of a Simpler Method*[6] *Employing Citrate as Anticoagulant.* The aim of the Rourke-Ernstene sedimentation technique is to avoid the use of citrate; results are given in terms of the uniform sinking velocity, after correcting for cell volume. If the data presented in this article are correct, simpler methods of performing the sedimentation test, using citrate as anticoagulant, should yield essentially the same result as the Rourke-Ernstene technique, although the results will be expressed in terms of a different numerical scale.

A comparison of results from the Rourke-Ernstene technique and from the the Hambleton-Christianson[6] technique was made on duplicate blood samples taken from each of 55 patients. The results (Fig. 6) indicate that a fairly consistent relation exists between the results of the two methods, the correlation coefficient being 0.92 ± 0.02. In no case did the results suggest that the Rourke-Ernstene technique gave more valuable information than was obtained by the other method.

In the case of one patient (W. J. M.), the results of the two methods did not have the anticipated relation to one another. The results of three successive tests are indicated in Figure 6,* as in all cases the C. S. R. by the Rourke-Ernstene technique is much lower than would be expected from results with citrate as anticoagulant. Dr. B. J. Robinson kindly furnished the following details of the patient.

Case Abstract. "W. J. M., farmer, aged 28, tuberculosis of 1 year's duration, with fatigue, loss of weight, frequent small hemoptyses, cough and expectoration. On admission, patient had definite bilateral lung involvement, apex to fourth anterior rib on both sides, with excavation in right upper lobe. Sputum positive. Bilateral pneumothorax established, with fairly select upper lobe collapse on each side. No great change in symptoms observed. A recent examination fails to show any appreciable lesions as far as the lung is concerned. Sputum is positive by concentration test. The prognosis is poor."

* In all three tests the *observed* S. R.'s, whether with citrate or heparin as anticoagulant, remained much more constant. The wider differences in the *corrected* S. R. results shown in Figure 6 are due to changes in cell volume, and these corrected results do not correspond to the condition of the patient, which remained relatively unchanged. This is an example where correction for cell volume is a disadvantage, and leads to results which are of less value.

The sedimentation rate obtained when using citrated blood is in better accord with this patient's condition than is the lower sedimentation rate indicated by the Rourke-Ernstene technique.

Use of Oxalate in Place of Citrate. Some workers prefer to use oxalate in place of citrate as anticoagulant. The disadvantage of oxalate, whether used dry or in isotonic solution, is that the sample should be used within 1 hour of drawing the blood,[1] whereas citrated blood retains its sedimentation rate unchanged over a period of 4 or 5 hours. If dry oxalate or citrate is used as anticoagulant in place of isotonic oxalate or citrate solution, (1 vol. to 4 vols. of blood), the numerical results of the test are altered to the extent indicated in Figure 2 of this article.

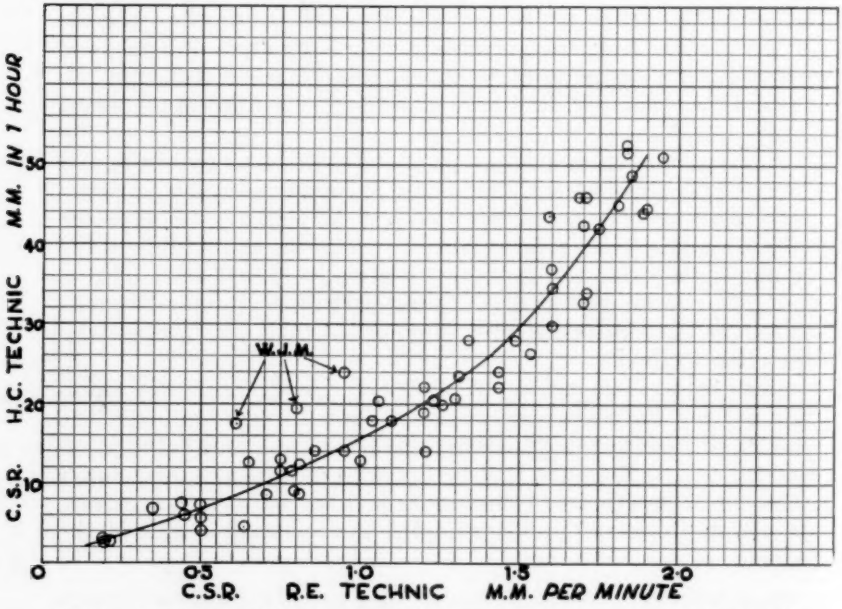

FIG. 6.—Comparison of the C. S. R. by the Rourke-Ernstene method to the C. S R. by the Hambleton-Christianson method.

Summary. The data obtained at this tuberculosis sanatorium indicate that the sedimentation test remains today essentially what it was when Fahraeus introduced the test in 1918, and that all the significant clinical data which may be obtained by sedimentation procedures can be found by a single 1-hour reading by the Westergren technique. Alleged improvements upon the Westergren sedimentation method have been presented which appear theoretically correct, *e. g.*, correction for cell volume, the use of heparin in place of citrate, and graphic methods of recording the results. Instead of making

the test more valuable, these changes have the reverse effect, either by leading to results of less clinical value, or by making the test more tedious to perform or less clear to interpret without increasing its clinical value. Hence it is recommended that the Westergren method, by reason of its simplicity, reliability and priority, should be adopted as the standard method of performing the sedimentation test.

In conclusion, those who use the Westergren technique should keep in mind that due to the narrow bore of the tube it is all the more important to see that the tubes are perfectly vertical during the test.[10]

The authors are indebted to Dr. D. W. Crombie, Medical Superintendent, at the Queen Alexandra Sanatorium, and Dr. J. L. Blaisdell, Director of the Morgan Laboratory, for their interest and coöperation in this work. The technical assistance of Mr. R. Comrie is also acknowledged.

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NOTE ON ERYTHROBLASTIC SPLENOMEGALY OCCURRING DURING PREGNANCY.

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Extramedullary erythropoiesis occurs in association with certain diseases of the bone marrow, such as erythroblastic anemia[1] and carcinomatous replacement of the bone marrow;[4] but it is unusual to find hematopoietic foci in the spleen, liver and lymph nodes without conspicuous disease of the bone marrow. Emile-Weil, Isch-Wall, Perles and Seemama[2] have reported 4 cases that they term cryptogenic erythroblastic splenomegaly. The patients

were adults; 2 had anemia and 2 slight polycythemia. The total leukocyte count varied from 4400 to 29,000, with from 6.5 to 15% of myelocytes. Puncture of the spleen and liver showed many megaloblasts and normoblasts, while puncture of the bone marrow revealed only a slight preponderance of normoblasts.

The present case with autopsy is described in order to define more accurately the morphological alterations of the condition. It also is the first case reported during pregnancy.

Case Report. A colored woman (No. 143468), aged 20, was first admitted to the Prenatal Clinic of the New York Lying-in Hospital on July 3, 1936. The expected date of confinement was November 28, 1936. The past history was negative except for frequent attacks of rheumatic fever.

On the first admission, with a normal 5-months' pregnancy, the physical examination was negative. Hemoglobin was 74% and the Wassermann test, negative. In view of a former positive Wassermann test, a total of 3.15 gm. of arsphenamine and 0.2 gm. of bismuth were administered during the succeeding month.

Between September 5 and 19, 1936, the patient suffered from a lobar pneumonia involving the left lower lobe. Hemoglobin was 60%, and white blood cells 25,000, with 63% neutrophils and 10% myeloblasts. The cell volume was 23%. Type XVIII pneumococcus was cultured from the sputum. With symptomatic treatment and a transfusion there was an uneventful recovery.

The patient was readmitted to the hospital on October 24, 1936, because of frequency of urination, dysuria, and blood-tinged urine for a period of 24 hours. No abnormality was found by physical examination. Hemoglobin was 70%, red blood cell count 3,040,000, white blood cell count 8480. The urine showed 3+ albumin and numerous red blood corpuscles. Upon the basis of intravenous pyelograms and cystoscopic examination a diagnosis of subacute cystitis was made. Under irrigation treatment the amount of blood in the urine gradually diminished.

Labor began at 6 A.M. on November 16, 1936. The cell volume at this time was 27%. Progress was satisfactory, but the patient was so uncooperative and excitable that she was given morphine sulphate 0.010 gm. and scopalamine 0.0001 gm. on one occasion and rectal ether (90 cc. of ether and 0.6 gm. quinine) on two occasions.

After 15 hours of labor the patient delivered spontaneously by vertex presentation a normal female infant weighing 3000 gm. The third stage was normal and the placenta was delivered by the Schultze mechanism 8 minutes later with a measured loss of blood of 100 cc. An episiotomy was repaired without difficulty and the patient received nitrous oxide and oxygen anesthesia with 15 cc. of ether. At 10.15 P.M., or 1 hour after delivery, the pulse was 76 but feeble, and the blood pressure could not be obtained. The pulse then rose to 120 and was of poor volume. She was restless and had to be restrained. The skin was warm. At 10.50 P.M., the pulse was 148 and the respiratory rate 68. The only complaint at this time was epigastric pain. Examination of the heart and lungs was negative. There was no evidence of internal bleeding. In spite of intravenous therapy and cardiac and respiratory stimulants the condition did not improve. A transfusion was started at 12.42 A.M., but 7 minutes later respirations ceased, 3 hours and 30 minutes after delivery.

Autopsy. The body was that of an adult colored female. The breasts were well developed. A small quantity of bloody fluid issued from the vagina.

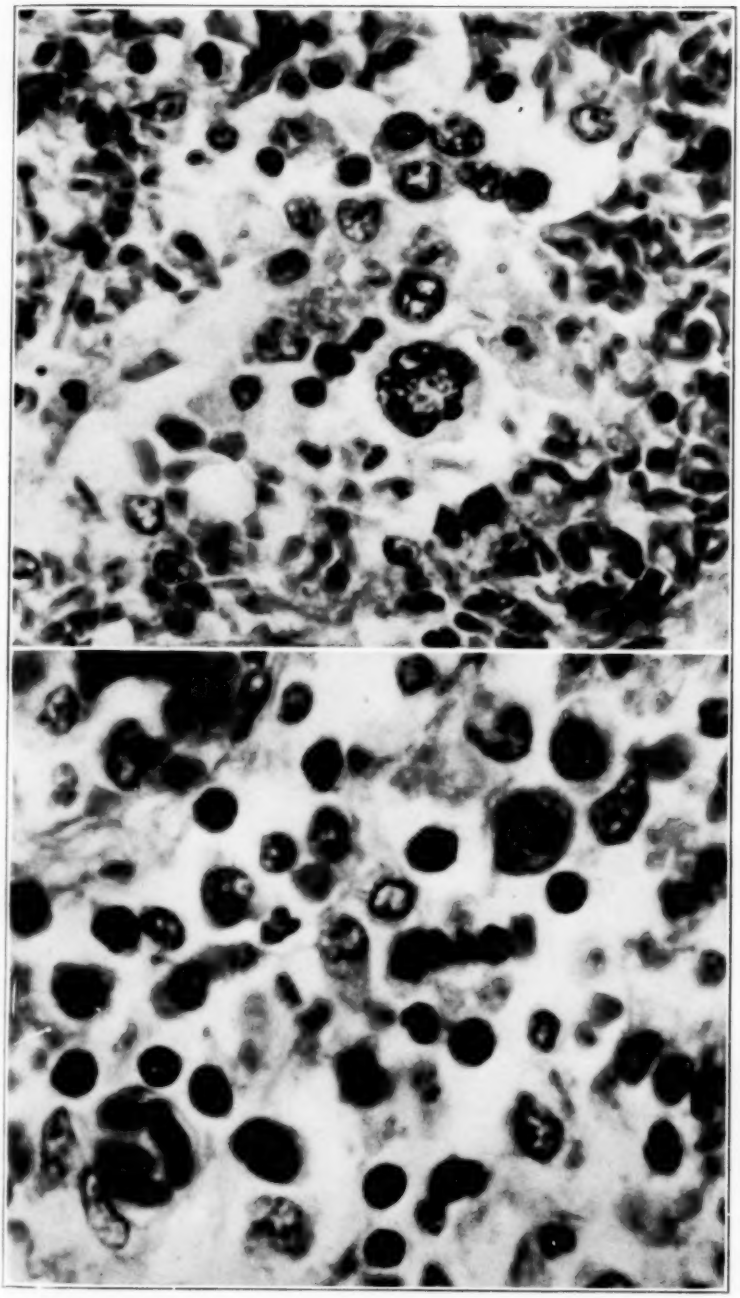

FIG. 1.—A small focus of erythrogenic tissue in the spleen. There are erythroblasts, megaloblasts and one megakaryocyte. (× 850.)

FIG. 2.—Infiltration of a lymph node with immature myeloid cells. (× 1100.)

The superficial lymph nodes of the axillary, cervical and inguinal groups were enlarged and soft. The cut surface was pinkish gray and finely granular. The visceral lymph nodes of the mediastinal, periaortic and mesenteric groups were of a similar appearance. The bone marrow of the vertebral bodies was reddish gray, of the ribs and sternum red, and of the midtibia reddish gray with little visible fat.

The spleen weighed 1190 gm., was firm in consistency and grayish red in color. The Malpighian bodies were indistinct and the pulp bulged slightly from beneath the capsule.

There were fibrous pleural adhesions laterally and posteriorly over both lungs but none over the apices. The lungs were crepitant throughout except for an area 2 cm. in diameter in the left lower lobe where the tissue was firm, gray and granular. There was a linear fibrous scar, 20 by 4 by 4 mm., in the right upper lobe. All of the tracheobronchial lymph nodes on the right side and the left inferior group contained caseous nodules which varied from 2 to 6 mm. in diameter. Roentgen ray examination revealed a calcified nodule in the left lower lobe and in a left inferior bronchial lymph node.

The liver weighed 2650 gm., was brown in color and firm in consistency. On section, the architecture was clearly visible as yellowish brown portal areas and reddish brown central areas.

The cortices of the kidneys contained numerous small abscesses. The pelves were slightly dilated, and the mucosa of the pelves, ureters and bladder was congested and swollen.

The uterus was large and the wall thickened, but there were no changes not characteristic of a 6-hour postpartum uterus. The tubes, ovaries and vagina were normal. The pituitary gland weighed 900 mg.

A smear of the blood in the hepatic veins showed many myeloblasts and myelocytes, together with normal cellular elements. There were no nucleated red blood cells. A culture of the spleen remained sterile after incubation for 7 days.

Microscopic Examination. The white pulp of the spleen is relatively decreased in amount. The red pulp is relatively increased, largely due to distention of the sinusoids with red blood cells. There is no increase in the reticulum or endothelial cells. Throughout the red pulp there are small foci composed of two cell types (Fig. 1). One is a small cell, 8 to 10 microns in diameter, with a round, hyperchromatic, dense nucleus and a narrow rim of acidophilic cytoplasm. Rarely there is more abundant cytoplasm and the nucleus is less chromatic. The second is a larger cell, 12 to 18 microns in diameter, round or polygonal, with a light staining vesicular nucleus and abundant, lightly acidophilic or neutrophilic cytoplasm. A few of the latter cells have from 2 to 3 nuclei. Occasionally these two kinds of cells are present in the same focus. They are interpreted as stages in the development of the red blood cells, the first as the normoblast and normocyte, and the second as the megaloblast. Scattered throughout the red pulp, usually not associated with the cellular foci, there are large cells, 50 to 60 microns in diameter, with four to eight hyperchromatic central nuclei. These cells are interpreted as megakaryocytes.

The lymph nodes throughout the body show conspicuous edema and congestion. The follicular architecture is entirely obliterated, and the blood-vessels are congested. The reticulum fibers of the tissue cords are separated and the interstitial spaces partially filled with lymphocytes, a moderate number of myelocytes and a few myeloblasts, normoblasts and megaloblasts (Fig. 2). Occasionally the erythrogenic elements are collected in small foci but the myelogenic elements are diffusely distributed. There is a rare multinucleated giant cell of the megakaryocytic type.

The individual liver cells are separated from one another but the cyto-

plasm and nuclei are normal in appearance. The sinusoids are narrow and filled with red blood cells and a few myelocytes and neutrophils. There is an occasional erythrogenic focus similar to those in the lymph nodes and spleen.

In the bone marrow of the tibia, vertebral bodies, ribs and sternum, there is a slight increase of erythrogenic and myelogenic tissue, but there are no atypical cells and no evidence of delayed maturation. In none of the hematopoietic organs is there pigmentation nor evidence of phagocytosis of red blood cells.

The lungs show an organizing pneumonia in the right lower lobe and a few tubercles in the left lower lobe. The kidneys show no pathologic change other than the abscesses described. The blood-vessels of the lungs and kidneys are dilated and filled with red blood cells and many myelocytes.

Sections of the placenta show a few immature myeloid cells in the maternal vessels. The cells in the fetal vessels of the placenta are normal.

Pathologic Diagnosis. Anemia; slight hyperplasia of the erythrogenic and myelogenic elements of the bone marrow; splenomegaly; hepatomegaly; erythroblastic foci in the spleen, liver and lymph nodes; myeloid infiltration of the lymph nodes; leukostasis of immature myeloid cells in the vessels of the lungs, kidneys, and liver; organizing pneumonia of the left lower lobe; pleural adhesions; postpartum uterus; hypertrophy of the pituitary gland; hypertrophy of the breasts; cystitis; ureteritis; pyelonephritis with multiple abscesses; congestion of the liver, spleen and kidneys; fibrous scar of the right upper lobe; conglomerate tubercles in the right lower lobe; fibrocaseous tuberculous nodules of the tracheobronchial lymph nodes; calcified tuberculous nodules in the right lower lobe and tracheobronchial lymph nodes.

Discussion. The essential alteration of the hematopoietic tissue is an enlargement of the spleen, liver and lymph nodes with the formation of erythrogenic foci. The changes resemble those of myeloid leukemia, erythroblastic anemia of Cooley and pernicious anemia; but there are structural changes or other factors entirely inconsistent with each of these diseases. The case in its essential features corresponds with those reported by Emile-Weil and his associates,[2] although the autopsies in their cases are so incompletely described that an exact comparison cannot be made.

The pathogenesis and etiology of the changes cannot be definitely outlined and must await study of additional cases. In the present case there are several factors which may be significant. During pregnancy the metabolism of iron is increased and the occurrence of anemia is more common than in non-pregnant women.[3] An additional slight disturbance of the erythrogenic tissue might therefore result in conspicuous alterations. There is abundant evidence of infection in the present case: a lobar pneumonia 2 months before death, latent pulmonary tuberculosis, urinary infection with multiple abscesses of the kidney, and a history of repeated attacks of rheumatic fever. The history of a positive Wassermann test is of doubtful significance because of the absence of anatomical changes of syphilis. It is possible that one or more of the infections, combined with pregnancy, induced the alterations of the hematopoietic tissue.

Summary. A case of conspicuous extramedullary erythropoiesis with splenomegaly but without significant alteration of the bone marrow is reported. It was associated with lobar pneumonia during pregnancy but there is insufficient evidence to determine the etiology and pathogenesis.

We wish to thank Dr. Eugene L. Opie and Dr. Jacob Furth for assistance in the study of this case.

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SEDIMENTATION RATES OF SICKLED AND NON-SICKLED CELLS FROM PATIENTS WITH SICKLE CELL ANEMIA.

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Abundant work has shown that there is a definite correlation between the tendency of erythrocytes to form rouleaux and their sedimentation rate.[1,2] It has also been demonstrated that the proportion of red blood cells to plasma influences the rate of settling; and this has led to the practice, followed by many, of "correcting" the observed sedimentation rate when there exists a reduction below normal in the number of circulating erythrocytes.[5,7] The material presented below is of interest because wide variation in the speed of settling of red cells of the same blood has been produced without altering their relative number. It was found that sickled erythrocytes from patients with sickle cell anemia and the sickle cell trait did not form rouleaux and in this condition did not sediment appreciably in one hour's time, whereas non-sickled cells from these same patients formed rouleaux and sedimented.

Method. The number of sickled erythrocytes in freshly drawn blood from patients with sickle cell anemia and the sickle cell trait was greatly increased by the well-known method of subjecting the blood to carbon dioxide.[3] Five cc. of oxalated blood (4 mg. of potassium oxalate and 6 mg. of ammonium oxalate per 5 cc.[7]) were divided equally between 2 small Erlenmeyer flasks. The blood in 1 flask was subjected to a gentle stream of carbon dioxide for 1 or 2 minutes and the flask was then stoppered. The blood in the other flask was similarly treated with oxygen. Samples of blood from each flask were examined in wet cover glass and slide preparations for the per cent of sickled cells and for the presence or absence of rouleaux formation. One Wintrobe sedimentation tube was filled with

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each sample and sealed. Observations of the sedimentation of the erythrocytes were made at 5-minute intervals. Cell volume determinations were then made. The white cells did not separate in a distinct layer in the tube containing sickle cell blood which had been subjected to carbon dioxide, because there had been almost no sedimentation before the tube was placed in the centrifuge. For this reason, it was necessary to obtain the volume of packed white blood cells from the corresponding oxygenated tube; this value was then subtracted from the total volume of packed cells in the tube of blood treated with carbon dioxide to obtain the exact volume of packed red blood cells in that tube. No correction for anemia was made in any reading given below.

Results. The accompanying table contains data obtained with the blood of 2 patients with sickle cell anemia, 1 with the sickle cell trait, and a representative control. Similar results were obtained with blood from 2 other patients with sickle cell anemia. Subjection of blood from these patients to carbon dioxide produced about 50% sickling, whereas less than 10% sickling was present when the same blood had been treated with oxygen. No rouleaux were observed to form in the blood treated with carbon dioxide and this blood sedimented less than 1 mm. in 1 hour; the oxygenated blood, on the other hand, formed good rouleaux and sedimented from 23 to 70 mm. in the same length of time.

TABLE 1.—SEDIMENTATION RATE OF SICKLED CELLS.

Patient:	Sickle cell trait.		Sickle cell trait.		Sickle cell anemia (quiescent).		Control (atrophic arthritis).	
R.B.C. per c.mm.:	2,810,000.		3,900,000.		Not done.		4,180,000.	
R.B.C. treated with:	O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.
Smear:	Rare sickled cells; field filled with rouleaux.	47% sickled; no rouleaux.	No sickled cells; good rouleaux formation.	53% sickled; no rouleaux.	9.5% sickled: few rouleaux, single cells and clumps	45.5% sickled; no rouleaux.	Field filled with rouleaux; few single cells.	Field filled with rouleaux; few single cells.
Time (min.).	Sedimentation (mm.).		Sedimentation (mm.).		Sedimentation (mm.).		Sedimentation (mm.).	
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	6.0	0.0	1.5	0.0	0.0	0.0	0.0	0.5
10	19.0	0.0	9.5	0.0	1.7	0.0	1.0	1.7
15	33.0	0.0	18.0	<1.0	3.0	0.0	5.0	5.0
20	45.0	<1.0	25.0	<1.0	5.0	0.0	12.0	9.0
25	53.0	<1.0	31.5	<1.0	8.0	<0.5	22.0	14.2
30	59.0	<1.0	36.5	<1.0	10.0	<0.5	31.0	21.2
35	63.0	<1.0	42.0	<1.0	12.0	<0.5	38.5	29.0
40	66.0	<1.0	44.7	<1.0	14.0	<0.5	44.5	36.2
45	68.0	<1.0	48.2	<1.0	16.5	<0.5	48.7	40.5
50	69.0	<1.0	51.5	<1.0	19.0	<0.5	51.2	44.5
55	69.6	<1.0	53.8	<1.0	21.0	<0.5	52.7	47.0
60	70.0	<1.0	56.0	<1.0	23.0	<0.5	53.5	48.7
Vol. % packed red blood cells	20.3	27.3	26.0	31.6	22.0	25.0	35.0	38.0

Control determinations in addition to those presented in the table were made with blood samples taken from a normal individual, a patient with chronic glomerulonephritis, a patient with metastatic malignancy, and a patient with ulcers of the leg. No difference was detected between the appearance of the rouleaux in the samples subjected to oxygen and in those treated with carbon dioxide. The erythrocytes sedimented faster in the oxygenated tube by from 3 to 13 mm. in 1 hour; this result is consistent with that obtained by Ito.[4]

In all of the sickle cell and control bloods the volumes of packed red cells were consistently higher for the samples subjected to carbon dioxide than for those subjected to oxygen. It is well known that treatment of erythrocytes with carbon dioxide increases their volume.[6]

Summary. Sickled erythrocytes from patients with sickle cell anemia and the sickle cell trait did not form rouleaux and remained almost unsedimented after 1 hour's time, while non-sickled cells from the same patients formed rouleaux and sedimented.

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THE HEPATIC ORIGIN OF THE PLASMA-PROTHROMBIN OBSERVATIONS AFTER TOTAL HEPATECTOMY IN THE DOG.

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The liver has been regarded as the site of formation of prothrombin, chiefly because certain hepatotoxic agents, chloroform, carbon tetrachloride and phosphorus, cause a plasma-prothrombin deficiency, and because some patients believed to have severe damage of the liver have failed to respond to substrates containing large amounts of vitamin K and bile salts. Williamson and Mann[11] pointed out that the use of hepatic toxins is an unreliable method for the study of the functions of the liver. Direct experimental evidence on the relation of the liver to prothrombin synthesis is conflicting. Dam, Glavind, Lewis and Tage-Hansen[2] found an increase in blood coagulability in geese following exclusion of the

liver from the circulation. Warner[10] reported a moderate decline in plasma prothrombin concentration after partial hepatectomy in rats.

We have investigated the effect of total hepatectomy on the plasma-prothrombin concentration of the dog. Four dogs were hepatectomized by the three-stage method of Mann and 4 dogs by one-stage methods (Firor and Stinson,[3] and Markowitz, Yater and Burrows[7]). Prothrombin determinations were made by the method of Quick.[8] To estimate the effect of the associated drop in plasma fibrinogen on the prothrombin determinations a solution of fibrinogen prepared as described by Smith, Warner and Brinkhous[9] was added to certain specimens of plasma before recalcification. Plasma fibrinogen determinations were carried out according to the method of Foster and Whipple[4] on 5 of the dogs. To evaluate the effect of possible blood dilution, a very rough estimate of the hematocrit was obtained by centrifuging the oxalated blood in a No. 2 International centrifuge at 2000 r.p.m. for 10 minutes. The plasma-protein concentration was determined by the falling drop method of Barbour and Hamilton.[1]

All of the animals, except 1 which lived only 2 hours and received a transfusion of normal blood before the final specimen was taken, showed a fall in plasma prothrombin concentration (see Table 1).

TABLE 1.—CHANGES IN PLASMA PROTHROMBIN IN HEPATECTOMIZED DOGS.

Dog No.	Method of hepatectomy.	Survival time (hrs.).	Preoperative prothrombin (% normal).	Last prothrombin determination before death (% normal).	Decline from preoperative level (%).
379	Mann	6	80	10	87
877	Firor and Stinson	2	No prothrombin decline*		
891	Markowitz *et al.*	1	100	32 *	68
892	Markowitz *et al.*	6	82	35	57
904	Markowitz *et al.*	5¾	100	0	100
691	Mann	19	40	11	72
781	Mann	14	45	16	64
827	Mann	4	48	42†	12
					Average 58

* Dog had transfusion shortly before last specimen.
† Last specimen 2 hours postoperatively.

The effect on fibrinogen was determined in 5 dogs and was much less pronounced (Table 2).

TABLE 2.—CHANGES IN PLASMA FIBRINOGEN IN HEPATECTOMIZED DOGS.

Dog No.	Method of hepatectomy.	Survival time (hrs.)	Preoperative fibrinogen level (gm./100 cc. plasma).	Fibrinogen level before death (gm./100 cc. plasma).	Decline (%).
892	Markowitz *et al.*	6	0.508	0.407	20.0
904	Markowitz *et al.*	5¾	1.019	0.400	61.2
691	Mann	19	0.297	0.229	22.9
781	Mann	14	0.805	0.779	3.3
827	Mann	4	0.511	0.226	55.8
					Average 32.6

The curves obtained for prothrombin, fibrinogen, approximate cell volume, and plasma protein for the 2 animals that survived longest are shown in Charts 1 and 2. The relation of plasma prothrombin percentage, as determined with added fibrinogen, to prothrombin percentage without added fibrinogen, is shown in Chart 3. The 2 curves are very similar.

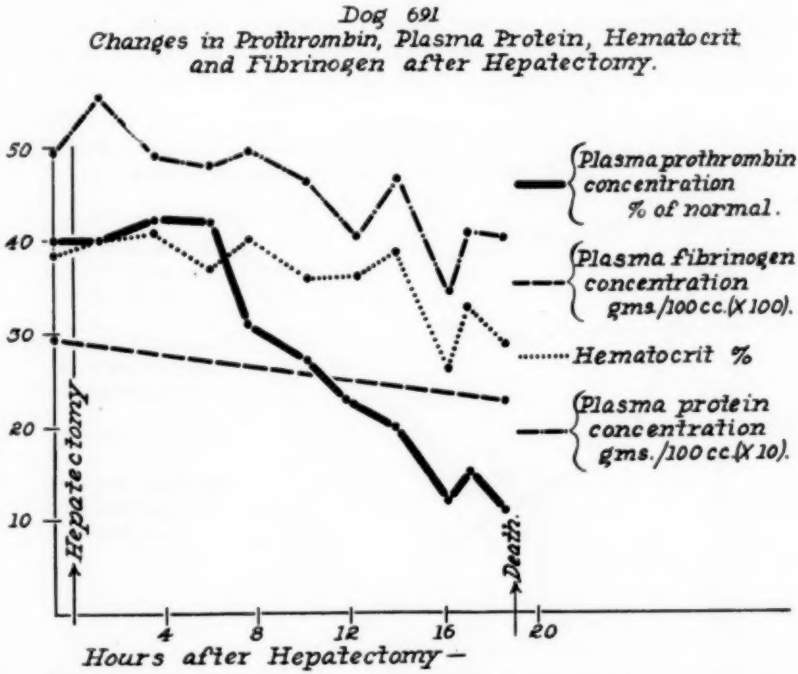

CHART 1.—Units for hematocrit, plasma-protein concentration, and plasma-fibrinogen concentration have been selected to demonstrate the relation of changes in these factors to changes in the concentration of plasma prothrombin.

Discussion. The data reveal irregular but definite declines in plasma-prothrombin concentration after total hepatectomy. The plasma-fibrinogen concentration also declined in a manner similar to that previously described by Jones and Smith[6] and others. That this was not of such a degree as to affect the prothrombin determinations seriously was shown by the observation that excess fibrinogen added to the specimens did not decrease the prothrombin times as determined by the Quick[8] method (Chart 3).

The consistently low plasma-prothrombin values in the dogs coming to the third stage of the multiple stage hepatectomy could be due to one or more of several factors which we plan to investigate.

We believe that the rapid decline in plasma-prothrombin concentration after hepatectomy is evidence that the site of prothrombin

synthesis has been removed. That it might be the result of a rapidly developing vitamin K deficiency due to the exclusion of bile from the intestinal tract is unlikely because Hawkins and Brinkhous[5] found that 2 to 3 months were required for prothrombin deficiency to develop in dogs as the result of biliary fistula. Certainly the animals operated upon by the one-stage technique could have no deficiency of the vitamin K stores. This is demonstrated by the fact that dogs taken from our stock have undergone anastomosis of the gall bladder to the renal pelvis and subsequent diversion of all bile from the intestinal tract for as long as 15 weeks without

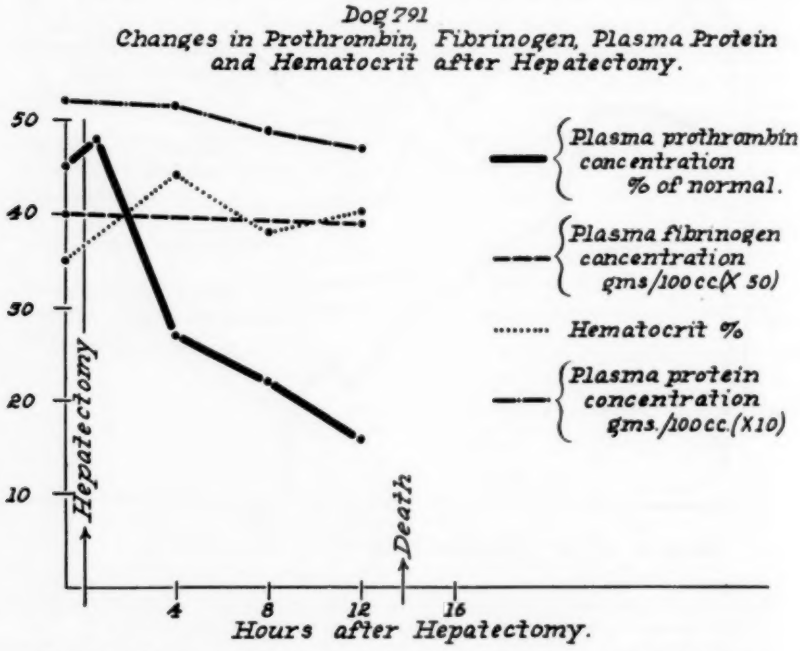

CHART 2.—Same units have been used for hematocrit, plasma-protein concentration and plasma-prothrombin concentration as in Chart 1; unit for plasma-fibrinogen concentration has been doubled.

the development of a prothrombin deficiency. Furthermore, dogs with recently established biliary fistulæ have been able to regenerate prothrombin after a deficiency of this factor was produced by chloroform anesthesia.

In order to determine whether the drop in plasma-prothrombin concentration following hepatectomy might be produced by factors incidental to the operation a number of control animals were studied. It was found that hemorrhage, plasmapheresis, laparotomy for other procedures, and ether anesthesia for 3 hours, failed to produce plasma prothrombin deficiency in the normal stock dogs.

Conclusions. 1. A rapid decline in plasma-prothrombin concentration as determined by the method of Quick occurs in the dog after total hepatectomy.

2. A decline in fibrinogen concentration was also observed, but this was not sufficient to interfere with the prothrombin determinations.

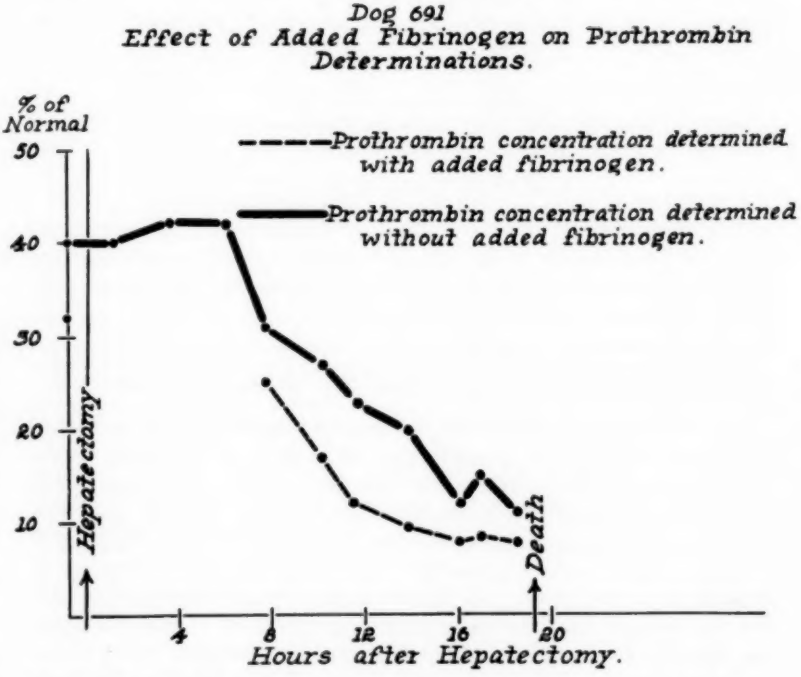

CHART 3.—Prothrombin concentration of the 2-hour, 4-hour and 6-hour specimens was not determined after the addition of fibrinogen.

3. The decline in plasma-prothrombin concentration could not be accounted for on the basis of anesthesia, hemorrhage, blood dilution, or laparotomy.

4. The liver is essential for the formation of prothrombin in the dog.

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THE EXPERIMENTAL PRODUCTION OF VITAMIN B_1 DEFICIENCY IN NORMAL SUBJECTS.

THE DEPENDENCE OF THE URINARY EXCRETION OF THIAMIN ON THE DIETARY INTAKE OF VITAMIN B_1*

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The antineuritic vitamin has been known to be present in human urine since 1918,[19] but quantitative estimation of the daily excretion of vitamin B_1 in the urine was not widely attempted until Birch and Harris[4] developed the bradycardia method in 1934. Since then Harris and his co-workers,[8,9] Roscoe,[23] and Baker and Wright[2a] have used this method in estimating the excretion of vitamin B_1 in the urine. As this method requires the maintenance of a rat colony, and the estimation requires 7 to 10 days, its use was limited to experimental nutritional laboratories. Moreover, the reliability of the bradycardia method has been questioned. Keresztesy and Sampson[15] have shown that vitamin B_1 depleted rats can utilize on the average only 60% of the vitamin adsorbed on the ingested acid clay. Robertson and Doyle[22] have pointed out that the bradycardia method in their hands gave inconstant results. Knott[16] has recently made balance studies on children, the food, urine and feces being assayed by a rat growth method.

Estimations of thiamin in the urine by chemical methods have been made in Jensen's laboratory[27a,b,c] and elsewhere[14,18,20,21,28] and by a fermentation method by Schultz and associates.[17,25,26] These investigators, however, did not, to our knowledge, maintain their subjects with weighed diets of constant composition and of known vitamin B_1 content. Other workers[1,6,13,24] gave to normal and hospital patients diets inadequate in vitamin B_1 but did not, to

* Preliminary report read before the fiftieth annual meeting of the American Physiological Society, April 1, 1938.

our knowledge, maintain their subjects with weighed diets of constant composition deficient only in vitamin B_1, nor did they determine daily the urinary excretion of vitamin B_1.

The recent development by Westenbrink and Goudsmit[27a] of a fluorimetric method for the determination of thiamin (vitamin B_1) in the urine has made the study of its urinary excretion a practical procedure. We have used their method for the determination of thiamin with slight modifications, consisting essentially of substitution of permutit for acid clay as the adsorbant of thiamin from dilute acidulated urine, and visual comparison of the unknown with a series of thiochrome* standards in the fluorimeter† instead of the electrical measurement of fluorescence by photoelectric cell and string galvanometer.

The purpose of this study was twofold: (1) The experimental production of symptoms and signs of vitamin B_1 deficiency in normal subjects while maintained with a constant weighed diet of known vitamin B_1 content and of probable adequacy in all other dietary essentials; (2) the determination of the thiamin excretion in the urine of these subjects during control, deficiency and recovery periods.

Methods. The vitamin B_1 poor diet used in this study (Table 1) is probably adequate for normal man except in vitamin B_1. The vitamin B_1/calory ratio was calculated from Cowgill's tables[5] to give a value of 1.

TABLE 1.—VITAMIN B_1 POOR DIET.

Article.	Grams or cc.	Article.	Grams or cc.
Lean beef*	100	Polished rice	50
Beets†	250	Honey	50
American cheese	100	Glucose	60
Apple or banana	200	Butter	100
White bread	150	Ginger ale	500
Macaroni	50	Candy	25
0.1 N hydrochloric acid	6	Liver fraction‡	15
Halibut liver oil	0.2	Ferrous sulphate	0.2
Cevitamic acid	0.05		

Estimated from Cowgill's tables to contain approximately carbohydrate, 380 gm., protein, 80 gm., fat, 140 gm., calories, 3150, vitamin B_1, 3150 mg. eq. of Cowgill (158 International Units or 0.474 mg. of thiamin) and a vitamin B_1/calory ratio of 1. Estimated from tables of Williams and Spies[29] to contain 0.360 mg. of thiamin, giving a thiamin/calory ratio of 0.11 and a thiamin/non-fat calory ratio of 0.2.

* Lamb or chicken could be substituted without significant change in vitamin B_1 or calories.

† Carrots, onions, cauliflower, egg plant, kohlrabi, green peppers, spinach, young string beans, tomatoes can be substituted without a significant change in vitamin B_1 and with but little change in total calories.

‡ Derived from 480 gm. of liver and free of vitamin B_1. By courtesy of Dr. Guy Clark, Lederle Laboratories, Pearl River, N. Y.

This ratio supplies 50% of Cowgill's predicted minimum vitamin B_1 requirement for a subject weighing 70 kg. The 100 gm. of butter in this diet was given a value of 800 mg. equivalent of vitamin B_1, which accounts for about 25% of the estimated vitamin B_1 content of this diet. We are

* Courtesy of Merck & Co., Rahway, N. J.

† Made by Hanovia Chemical and Manufacturing Co., New York City.

aware that this figure may not represent thiamin as such but the vitamin B_1 sparing properties of butter fat. The thiamin content as estimated from the tables of Williams and Spies[29] is 0.360 mg. giving a thiamin/calory ratio of 0.11 and a thiamin/non-fat calory ratio of 0.2.

Supplements of ferrous sulphate, cevitamic acid, halibut liver oil and a liver fraction were included in the diet to insure its adequacy in iron, vitamins A, B_2-complex, C and D. The supplement of hydrochloric acid, 3 cc. of which was given to each subject throughout the experiment, at the noon and evening meal, was included as a vehicle for the thiamin* which was added during the control and recovery periods only. By this method we hoped that the subjects would not be aware of the addition or withdrawal of thiamin. The diet was divided into 3 meals daily, except for the ginger ale, which was usually taken at night before retiring. The diet was accurately weighed and prepared by the Division's chief dietitian, Miss Bertha Weiss; it was consumed by all 5 subjects in its entirety at all times. They were not permitted any other source of calories. As large amounts of both natural and synthetic thiamin were available, we believed the experimental production of vitamin B_1 deficiency to a degree sufficient to produce early objective signs was not likely to be followed by permanent or irreversible damage. We thought it advisable, however, before using normal lay volunteers to demonstrate the safety of this procedure in subjects fully cognizant of the possible dangers. Consequently, the subjects of this study consisted of 2 of us (R. G. and J. G.) and 3 resident physicians. All subjects continued at their hospital duties during the term of the experiment.

The experimental observations on each subject were divided into three periods: control, deficiency and recovery. During the control period two subjects (R. G. and M. H.) received a weighed diet estimated to contain 2875 calories and 16.225 mg. equivalent (811 international units, 2.43 mg. as thiamin) of vitamin B_1. This diet supplied a vitamin B_1/calory ratio of 5.64 which is 2.75 and 2.68 times the minimum vitamin B_1 requirement[5] of these 2 subjects respectively. One subject (M. H.) complained so bitterly of hunger during the control period that on the ninth day each item of the diet was increased by 50%. The vitamin B_1/calory ratio was thus maintained constant. The other 3 subjects (M. T., A. M., and J. G.) during the control period were given the vitamin B_1 poor diet plus 2.16 mg. of synthetic thiamin. This gives a vitamin B_1/calory ratio of 5.64 which is 2.45, 2.89, and 3.52 times the minimum predicted vitamin B_1 requirement of these three subjects respectively. During the deficiency period all subjects received only the vitamin B_1 poor diet. In the recovery period, all subjects continued with the vitamin B_1 poor diet, and thiamin was added to the hydrochloric acid supplement in amounts designated on the chart of each subject.

The observations reported here were made at daily or frequent intervals throughout the control, deficiency and recovery periods. They include subjective symptoms, detailed physical examination, electrocardiographic tracings by the 3 standard leads, and estimation of the thiamin excretion on 10 cc. portions of accurate 24-hour urine samples collected under toluene, acidified, and kept in a refrigerator. Other observations not reported at this time include basal metabolism determinations, blood chemistry including vitamin B_1, hematologic studies and teleoroentgenograms at frequent intervals.

Results. Detailed data for each of the 5 subjects are given in Figures 1 to 6. They will be presented under 3 headings: the

* Courtesy of Merck & Co., Rahway, N. J.

early symptoms of vitamin B_1 deficiency; the early objective signs of vitamin B_1 deficiency; and the relation of the dietary intake of vitamin B_1 to the excretion of thiamin in the urine.

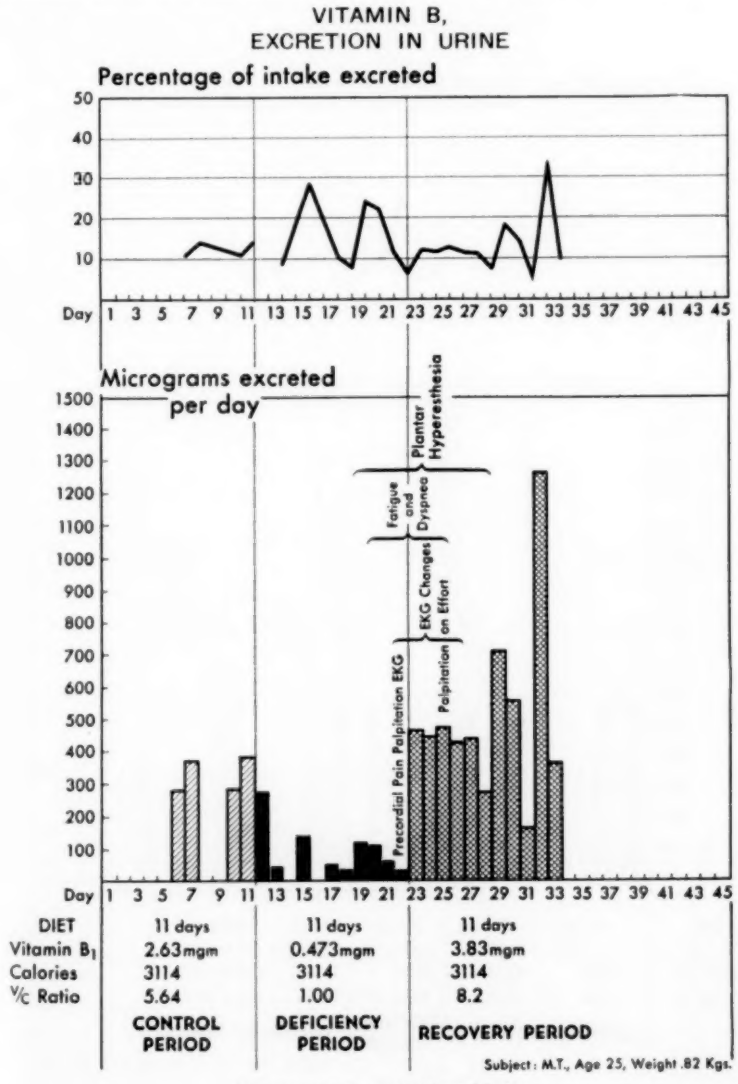

FIG. 1.—Data on Subject M. T.

The Early Symptoms of Vitamin B_1 Deficiency.—During the control period the subjects offered no complaints except that the 3 (M. T., J. G., and A. M.) who were maintained with the vitamin B_1

poor diet plus 2.16 mg. of thiamin daily all complained of constipation for the first 2 or 3 days. This condition was relieved spontaneously. The appetites of all subjects were maintained.

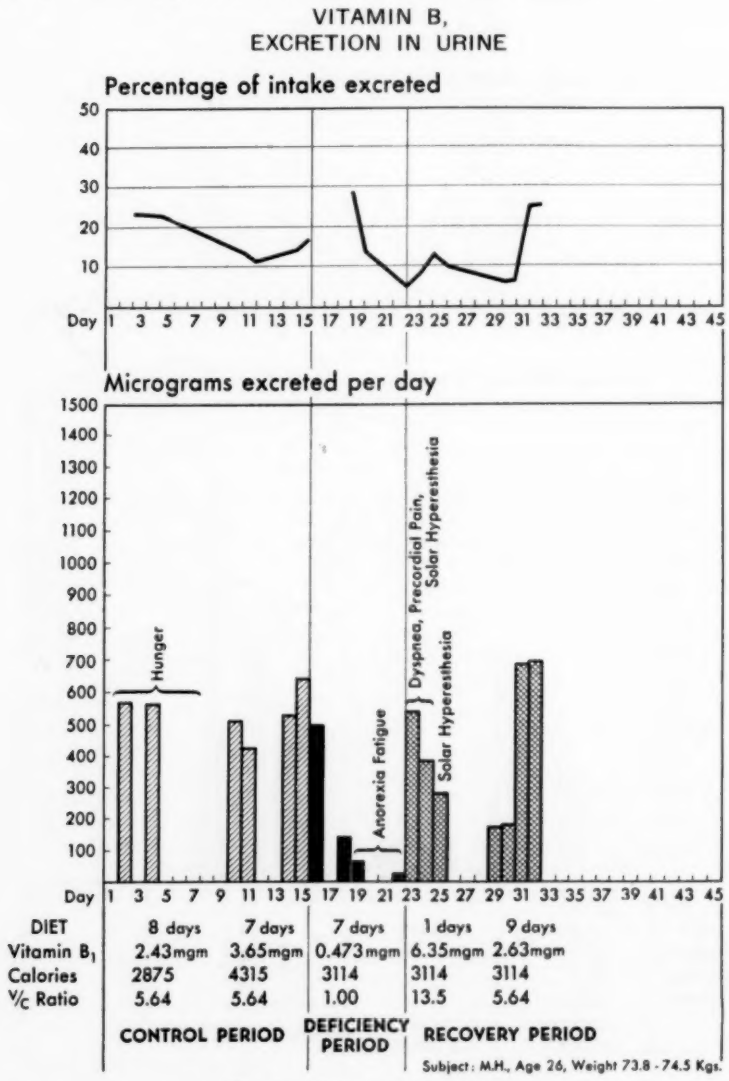

FIG. 2.—Data on Subject M. H.

Deficiency of vitamin B_1 was initiated by placing R. G. and M. H. on the vitamin B_1 poor diet, and by withdrawing the 2.16 mg. of thiamin from the hydrochloric acid supplement in the vitamin B_1

poor diet of M. T., J. G. and A. M. The first few days of the deficiency period were symptom free. On the 3d or 4th day the subjects began to complain of the monotony of the diet. All sub-

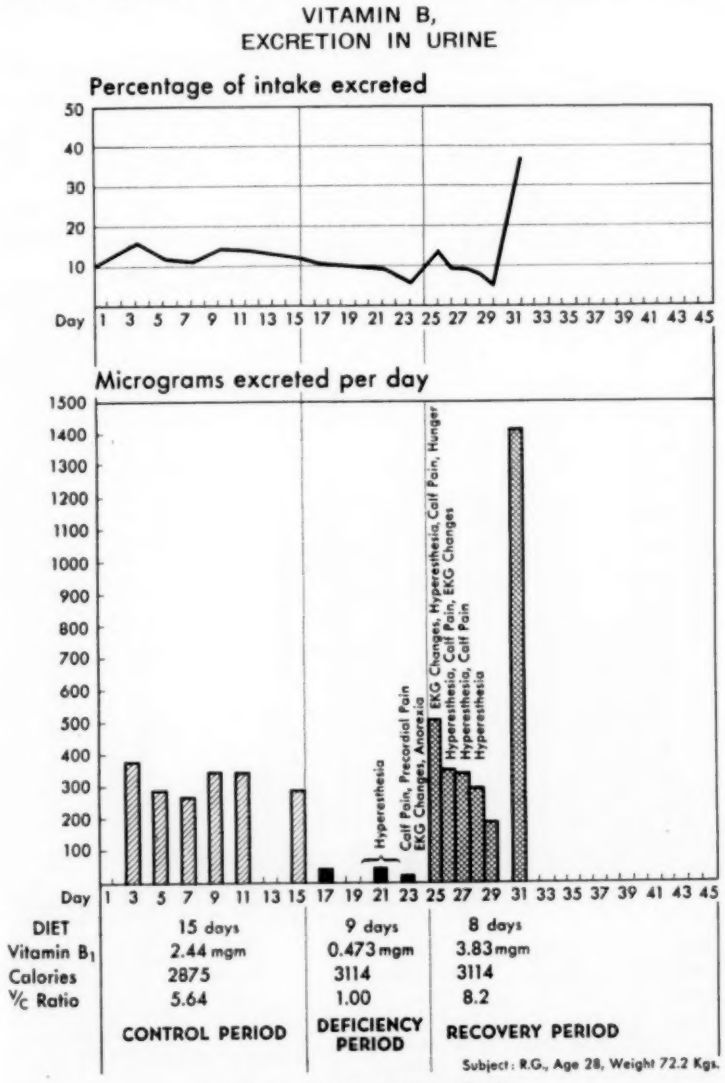

FIG. 3.—Data on Subject R. G.

jects developed symptoms, in 4 of whom they seemed definite. The symptom common to all 5 subjects was fatigue. It occurred as early as the 4th day of the deficiency period in M. H., the 8th

day in R. G., the 9th day in M. T., the 11th day in A. M., and by the 13th day in J. G. In the latter subject, this complaint disappeared spontaneously by the 18th day and did not reappear even

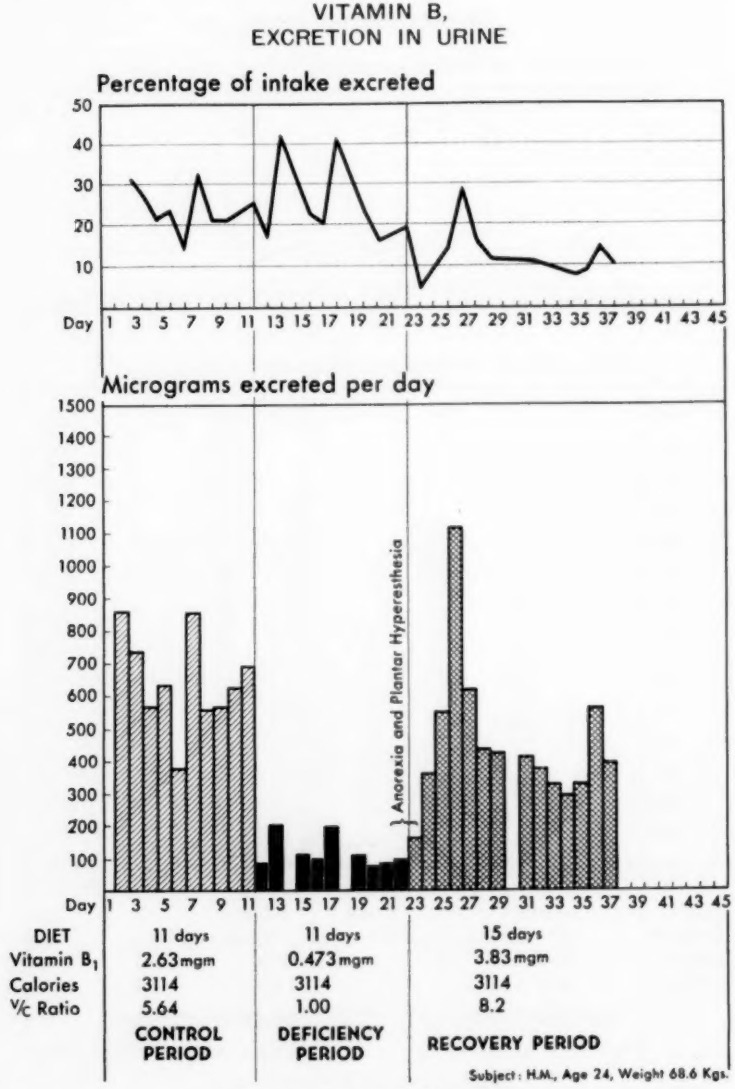

FIG. 4.—Data on Subject A. M.

though the deficient diet was continued for an additional 12 days. Four subjects complained of anorexia. It occurred as early as the 4th day in M. H., the 8th day in R. G., the 9th day in M. T., and

the 11th day in A. M. The anorexia seemed definite and it was only by considerable will-power that these 4 subjects consumed the diet in its entirety. Symptoms referable to the cardiovascular

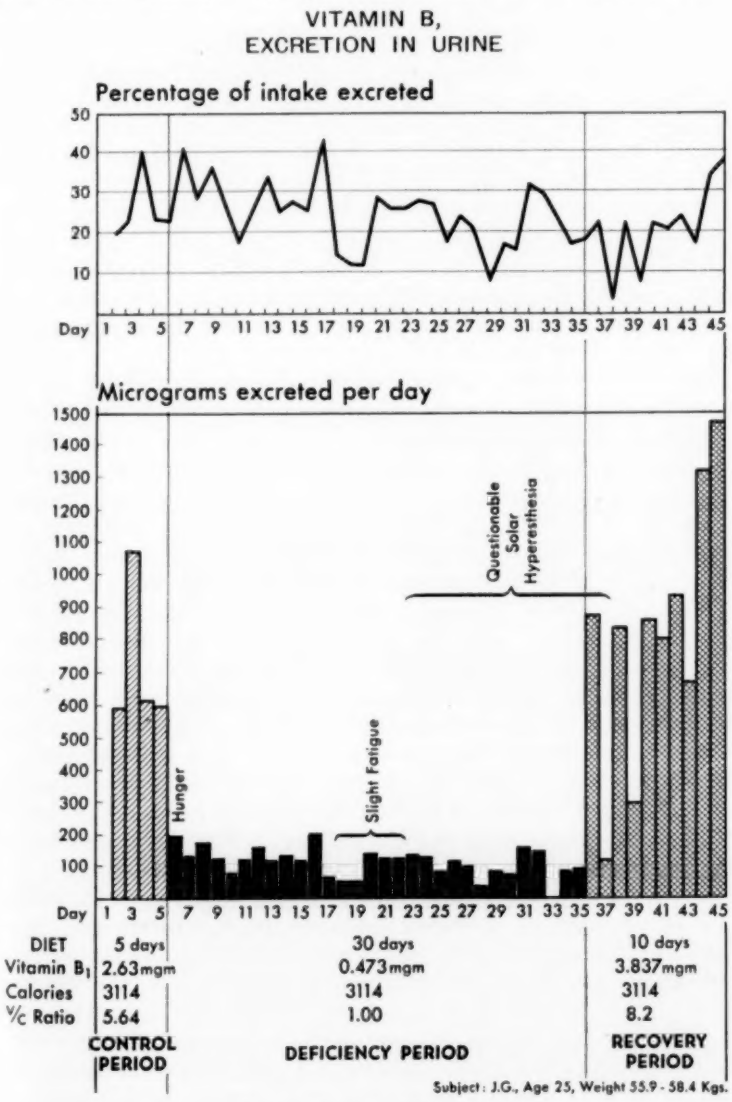

FIG. 5.—Data on Subject J. G.

system occurred in 3 subjects (M. H., M. T., R. G.). The symptoms were dyspnea on slight exertion in 2 subjects (by the 8th day in M. H., and by the 9th day in M. T.) and precordial pain in

3 subjects (by the fifth day in R. G., by the 8th day in M. T., and by the 11th day in M. H.), and palpitation in 1 subject (M. T. on the 12th day). These symptoms, though subjective, seemed definite. The precordial pain occurred on effort, lasted for 2 to 3 hours, was aching in character, precordial and substernal in location, and did not radiate to the shoulders, neck or arms. The dyspnea and fatigue in M. H. was so severe that he was unable on the 8th day of his deficiency period (1st day of recovery period) to walk up a flight of stairs without resting or to continue his duties as house physician.

Neurologic symptoms were observed in 3 subjects, all of whom complained of burning of the feet, especially at night. This symptom was first noted on the 5th day by R. G. and on the 8th day by M. H., and M. T. Cramps in the calf and feet muscles occurred in 2 subjects (M. H. and R. G.) by the 7th and 8th days respectively. Paresthesias were not noted by any subject.

The addition of thiamin to the vitamin B_1 poor diet, which marked the beginning of the recovery period, was followed by the prompt disappearance of all symptoms, in that no subject had any abnormal complaints after the 3d day of the recovery period. By this time anorexia had given way to hunger. The fatigue and lassitude which had been obvious to all who observed these subjects, was replaced by a feeling of well-being; burning of the feet, muscle cramps, precordial pain, dyspnea and palpitation were no longer present. The relief of symptoms occurred without the subjects being aware, except from the change in their own subjective feelings, that thiamin had been added to the hydrochloric acid supplement. The amount of thiamin added to the vitamin B_1 poor diet was 3.36 mg. daily except in the diet of M. H. This subject, whom we had to put to bed because of extreme fatigue and exhaustion, and who gave us considerable concern, received on the first recovery day 5.877 mg. of thiamin, which we calculated to be his accumulated deficit during the 7 days of his deficiency. For the remainder of his recovery period he was given 2.16 mg. of thiamin daily.

The Early Objective Signs of Vitamin B_1 Deficiency.—Objective signs of vitamin B_1 deficiency occurred in 4 subjects and were limited to hyperesthesia, calf tenderness, and changes in the electrocardiogram. Definite hyperesthesia was limited to the plantar surface of the feet in all these subjects except M. T., in whom by the 12th day (1st day of recovery period) it extended to the midcalf of both legs in a sock distribution. The hyperesthesia to pin prick or scratch was not associated with changes in temperature, tactile, two-point discrimination, position sense, or vibratory sensation. Calf muscle tenderness was elicited in only 1 subject (by the 8th day in R. G.). Changes in the electrocardiographic tracings were noted in 2 subjects. In R. G. (Fig. 6) the changes

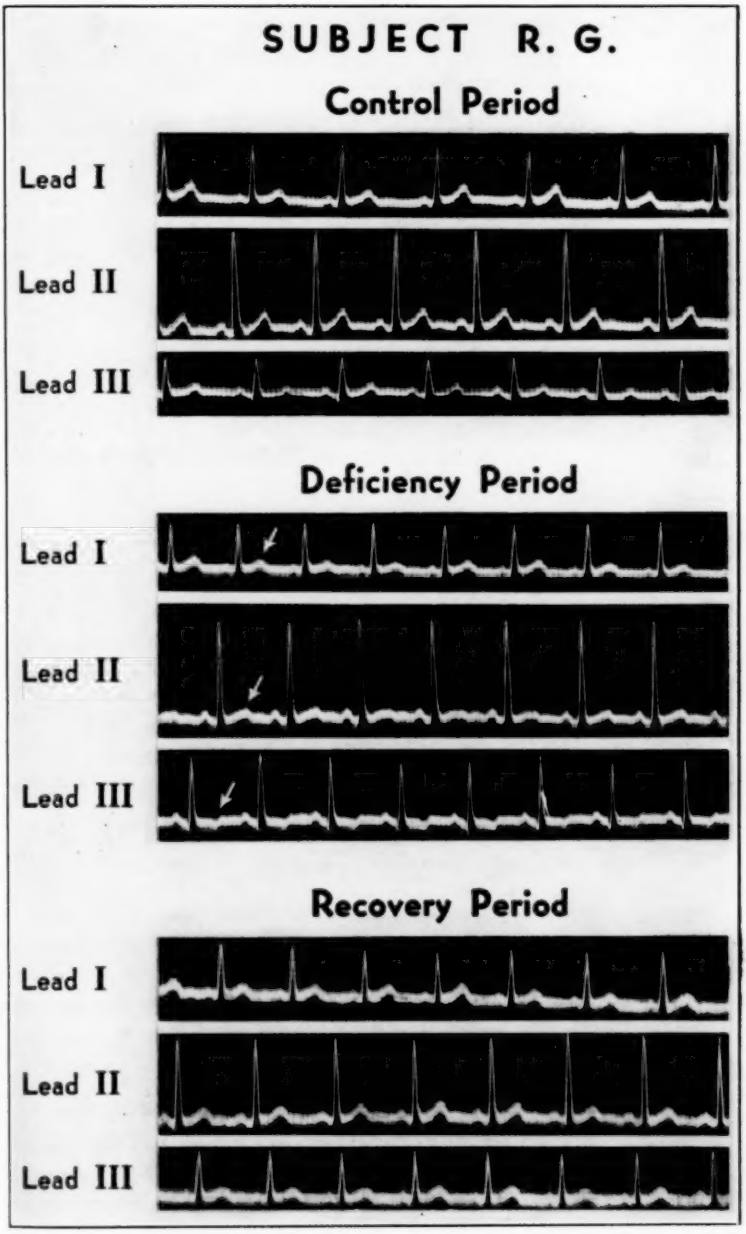
SUBJECT R. G.
Control Period
Lead I
Lead II
Lead III
Deficiency Period
Lead I
Lead II
Lead III
Recovery Period
Lead I
Lead II
Lead III

FIGURE 6.

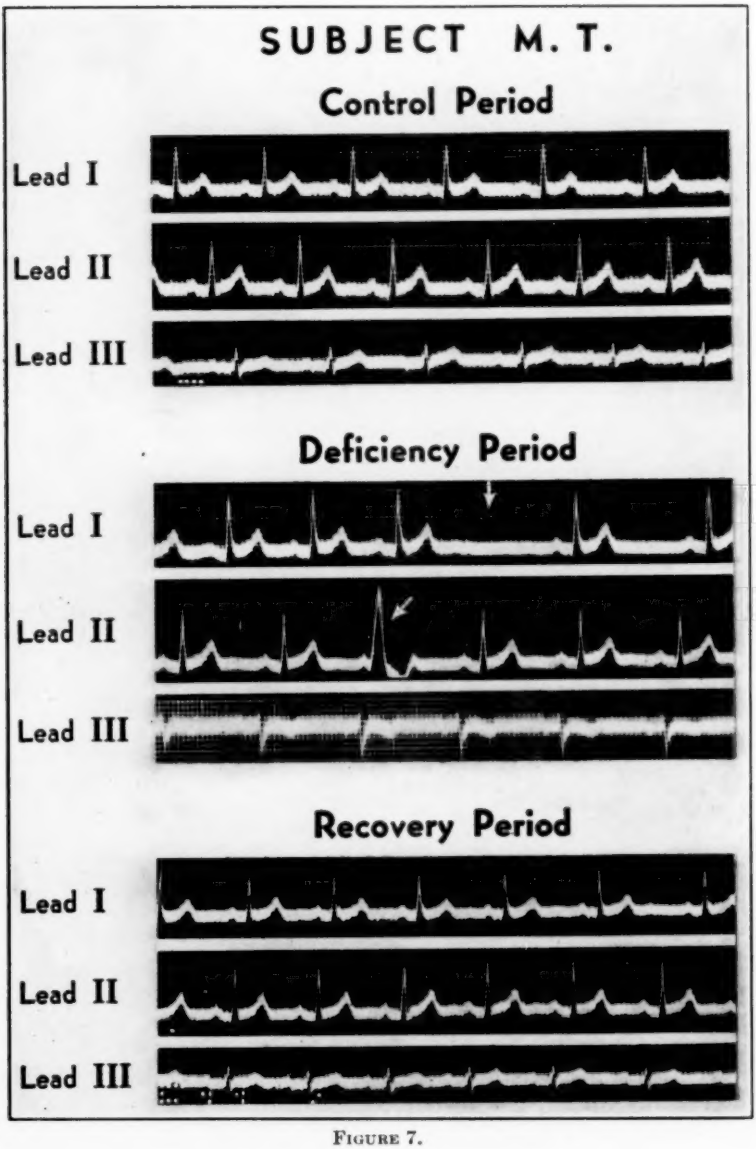
SUBJECT M. T.
Control Period
Lead I
Lead II
Lead III
Deficiency Period
Lead I
Lead II
Lead III
Recovery Period
Lead I
Lead II
Lead III

FIGURE 7.

occurred by the 8th day of the deficiency period and consisted of inversion of T_3. In M. T. (Fig. 7) electrocardiographic changes occurred by the 11th day of the deficiency period and consisted of sinus arrhythmia, sinus arrest, change in deviation of the electrical axis, and inversion of T_3. J. G., the smallest of the subjects, developed no definite objective sign of vitamin B_1 deficiency.

None of the following objective signs was noted: nystagmus, ataxia, changes in tendon reflexes, changes in the oral mucous membranes, dilated neck veins, epigastric pulsations, changes in size or shape of the heart, development of heart murmurs, changes in heart sounds, palpable liver, or peripheral edema.

When thiamin was added in the recovery period, the objective signs disappeared in the reverse order of their occurrence. Plantar hyperesthesia was the first to develop and was the last to disappear. It remained for 6 days in M. T., 4 days in R. G., 3 days in M. H., and 2 days in A. M. The electrocardiographic changes disappeared by the 3d recovery day in R. G. and by the 5th recovery day in M. T.

The Relation of the Dietary Intake of Vitamin B_1 to the Excretion of Thiamin in the Urine.—Inspection of the figures on the individual subjects (Figs. 1 to 5) immediately discloses that the urinary excretion of thiamin is roughly proportional to the dietary intake of vitamin B_1. It is also evident that the urinary excretion reflects, as a rule within 24 hours and always within 48 hours, changes in vitamin B_1 intake of the magnitude used in this study. This is true whether vitamin B_1 is added or removed from the diet.

In addition, it can be noted that during the deficiency period subjective symptoms did not occur unless the excretion of thiamin fell below 100 micrograms daily, and in 1 subject (R. G.) subjective symptoms did not occur until a level of about 30 micrograms was reached. The 3 subjects complaining of precordial pain and the 2 subjects showing electrocardiographic changes did not develop these symptoms or signs until the urinary excretion had fallen below 30 micrograms. During the recovery period, the symptoms and signs noted above did not promptly disappear when the urinary excretion of thiamin exceeded 100 micrograms daily.

The average thiamin excretion during the control period varied from 319 micrograms (R. G.) to 676 micrograms (J. G.), accounting for 13.1 to 25.7% of the estimated intake. During the deficiency period, omitting the first 3 days of this period as reflecting to some extent the intake during the control period, the average thiamin excretion varied from 35 micrograms (R. G.) to 108 micrograms (J. G.), accounting for 7.4 to 23% of the estimated intake. In the recovery period, the average thiamin excretion varied from 339 micrograms (R. G.) to 806 micrograms (J. G.), accounting for 11.7 to 21.1% of the estimated intake.

A considerable variation exists, it is evident, in the relative and absolute amounts of thiamin excreted. There is some indication (Table 2) that the smaller subjects (A. M. and J. G.) excreted more thiamin than the larger subjects (M. T., M. H., and R. G.) when maintained with the same vitamin B_1 intake. We have therefore studied the relation between the excretion of thiamin and the adequacy of the vitamin B_1 intake as judged by Cowgill's prediction formula[5] by a correlation of the thiamin excretion in micrograms with the ratio of vitamin B_1 intake/predicted minimum requirement (hereafter called the intake/requirement ratio). An intake/requirement ratio of 1 represents just a maintenance intake of vitamin B_1 and takes into consideration the individual's size and caloric intake. Such a correlation would naturally present considerable spread due not only to individual variations of an undetermined nature but also to a difference in the total metabolism of the individual subjects. When the intake/requirement ratio is between 2.5 and 5 there is excreted in our subjects at least 300 micrograms of thiamin daily. In this range, 1 subject averaged 800 micrograms daily. On the other hand, when the ratio was 0.4 to 0.65 the average excretion of thiamin was 110 micrograms or less daily. Insufficient data are at hand at the present time to judge whether these figures represent even a first approximation of the range of excretion of thiamin under the conditions of this study.

TABLE 2.—DATA ON INDIVIDUAL SUBJECTS BY AVERAGES OF PERIODS.

Subject.	Wt., kg.	Predicted minimum requirement as Vit. B_1/cal.	Period.	Vitamin B_1 intake as: Mg. thiamin.	Vit. B_1/cal.	Ratio. Intake / P.M.R.*	Average excretion of thiamin, mg. No. of determinations.	Mg.	% of intake.
M. T.	82	2.30	Control	2.633	5.64	2.45	8	0.377	14.3
			Deficiency	0.473	1.0	0.43	7	0.073	15.4
			Recovery	3.837	8.11	3.52	11	0.390	10.2
M. H.	74.5	2.10	Control 1	2.436	5.64	2.68	2	0.565	23.1
			Control 2	3.654	5.64	2.68	4	0.525	14.4
			Deficiency	0.473	1.0	0.47	2	0.044	9.3
			Recovery	2.633	7.65	3.64	6	0.394	15.0
R. G.	72	2.05	Control	2.436	5.64	2.75	6	0.319	13.1
			Deficiency	0.473	1.0	0.47	2	0.035	7.4
			Recovery	3.833	8.11	3.95	5	0.339	11.7
A. M.	68.5	1.95	Control	2.633	5.64	2.89	10	0.644	24.4
			Deficiency	0.473	1.0	0.51	7	0.110	23.2
			Recovery	3.833	8.11	4.15	14	0.447	11.7
J. G.	56	1.60	Control	2.633	5.64	3.52	5	0.676	25.7
			Deficiency	0.473	1.0	0.62	26	0.108	23.0
			Recovery	3.833	8.11	5.07	10	0.806	21.1

* P.M.R. = Predicted minimum requirement.

Comment.—The rapid production of both symptoms and objective signs of vitamin B_1 deficiency was in the beginning an unexpected result. Jolliffe, Colbert and Joffe[12] have estimated that "an individual may develop polyneuritis if the caloric need is satisfied by a diet free of vitamin B_1 for a period of a week, while every individual in our series had polyneuritis if the period of 'estimated absolute deficiency' was 21 days or more." The days of "estimated absolute deficiency" was calculated by multiplying the per cent of deficiency, as estimated from Cowgill's predicted minimum requirement, by the number of days over which the deficiency occurred. On this basis, our subjects accumulated the following number of days of "estimated absolute deficiency" before subjective symptoms developed: A. M. 5.4 days, M. T. 5.1 days, R. G. 4.2 days, M. H. 2.1 days. Objective signs were first observed after the following days of "estimated absolute deficiency": A. M. 5.4 days, M. T. 4.5 days, R. G. 4.2 days and M. H. 4.2 days. On the other hand, J. G. accumulated 11.4 days of estimated absolute deficiency without development of either subjective symptoms or objective signs.

In the previous study,[12] the calculated days of "estimated absolute deficiency" represented the minimum period over which the deficiency existed that produced definite signs of peripheral neuritis sufficient to fulfill the criteria for the diagnosis of polyneuritis as defined by Goodhart and Jolliffe.[7] In this study, the accumulated days of "estimated absolute deficiency" is considerably less than in the previous study. In the subjects of this study, a diagnosis of peripheral neuritis due to vitamin B_1 deficiency would not have been made by Jolliffe, Colbert and Joffe,[12] as the signs were not sufficient to fulfill the criteria for the diagnosis of polyneuritis as defined by Goodhart and Jolliffe.[7] On the other hand, the signs and symptoms developed with the vitamin B_1 poor diet and were relieved with the addition of synthetic thiamin alone; we therefore believe they can be attributed only to the lack of vitamin B_1.

That signs and symptoms may develop as rapidly as seen in this study with diets only moderately restricted (43 to 62% adequate) has many clinical implications. It suggests the possibility of a high prevalence of mild vitamin B_1 deficiency in the general population, which thesis has recently been elaborated by Jolliffe;[11] that vague ill-health characterized particularly by fatigue and persistent anorexia may be a manifestation of suboptimal intake of vitamin B_1; that when patients are treated with oral, parenteral or rectal feedings of dextrose or other vitamin free sources of calories, proper attention should be given to the vitamin B_1 supply, even though such a regimen extends over but a few days; that some of the errors in the diagnosis of coronary artery disease recently pointed out by Herrick[10] and Bean[3] may be eliminated by critical

evaluation of the diet, and that if the diet is found borderline or inadequate, or if the subject has other clinical signs of vitamin B_1 deficiency, a therapeutic trial should be instituted.

Harris, Leong and Ungley[9] have stated that when a steady state has been reached the excretion of vitamin B_1 "remains fairly constant at around 5 to 8 per cent of the intake, notwithstanding the wide variation in the latter." The excretion of thiamin as reported by these observers is lower than the results found in this study. Recalculation of certain of their results on the basis of an average recovery[15] by the rat of 60% of the ingested vitamin adsorbed on acid clay and of 1 international unit of vitamin B_1 being equivalent to 3.3 micrograms of thiamin, makes our results more comparable with theirs. For example, 7 of their "Normal Controls, Cambridge and London, May-October, 1935,"[9] not supplementing their diet by wheat germ, excreted 66 to 126 micrograms of thiamin daily. On the basis that their subjects had an average daily intake of 250 international units (825 micrograms of thiamin), which Harris and Leong[8] and Baker and Wright[25] have estimated as the average vitamin B_1 intake of middle class Englishmen, the daily excretion varied from 8 to 15.3% of the intake. On the basis of the same intake, the 8 "Normal Controls, Cambridge and London, February-March, 1937,"[9] not supplementing their diet with wheat germ, excreted from 10 to 22% of their intake. To a single subject whose diet they[8] estimate as averaging 250 international units of vitamin B_1, they gave an additional 110 to 1000 international units of vitamin B_1. Recalculation of these data indicates an excretion of 6 to 13% of the ingested vitamin B_1. Thus Harris' subjects excrete from 6 to 22% of their ingested vitamin B_1, while our subjects excrete from 7 to 25%. There is, therefore, not much difference in the range of excretion of thiamin as reported by us in this paper and the range reported by Harris and co-workers as recalculated by us. Most of our values, however, are in the upper levels and most of Harris' in the lower levels of this range of values. This apparent difference may be due not only to the difference in methods but to the difference in size of the subjects in the two studies and to the fact that our subjects consumed a constant weighed diet, while their subjects consumed an *ad lib.* diet the value of which was taken as "average."

Summary and Conclusions. We have experimentally produced in 4 of 5 normal human volunteers the signs and symptoms of early vitamin B_1 deficiency and studied in all the relation of the dietary intake of vitamin B_1 to the urinary excretion of thiamin. These subjects were maintained with accurately weighed diets of known content of vitamin B_1 and presumably adequate in all other essential elements of nutrition.

Definite symptoms and signs were observed in 4 of the 5 subjects while they were maintained with a vitamin B_1 poor diet. Symptoms were observed as early as the 4th day and objective signs as early as the 5th day, though 1 subject developed no definite symptom or objective sign in 30 days with a diet estimated to contain 62% of his predicted minimum vitamin B_1 requirement. The symptoms observed were fatigue and lassitude, anorexia, precordial pain, burning of the feet, dyspnea on exertion, muscle cramps and palpitation. The objective signs observed were skin hyperesthesia in a sock distribution, changes in the electrocardiogram, and calf muscle tenderness. The addition of thiamin alone to the vitamin B_1 poor diet caused all symptoms to disappear within 3 days and the objective signs within 6 days.

Our subjects excreted in the urine as thiamin 7 to 25% of the ingested vitamin B_1 (averaged periods). There was, under the conditions of this study, a good correlation in each subject between the vitamin B_1 intake and the urinary excretion of thiamin. Changes in the vitamin B_1 intake are early reflected by changes in the excretion of thiamin. With the same vitamin B_1 intake the excretion level varies from subject to subject but is roughly proportional to the adequacy of the diet as expressed by the ratio of vitamin B_1 intake/predicted minimum requirement.

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THE RELATION OF THE ADRENAL GLANDS TO THE ACTION OF THE RENAL PRESSOR SUBSTANCE.*

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Previous work[1,7] has shown that renal cortical tissue contains a substance (called "renin" by Tigerstedt and Bergmann[8]) which causes a well marked rise in blood pressure when administered intravenously to animals. Whether this substance plays any rôle in the control of vascular tone in the kidneys or elsewhere in health or disease is not definitely known. In view of its possible endocrine nature a study has been undertaken of the relationship of some of the endocrine organs to renin.

Methods. Rats were used. In one series of experiments various endocrine organs—either the adrenal glands, the hypophysis or the gonads—were removed. Several days later the sensitivity of these animals to a standardized extract of hog kidney was compared with that of normal rat. Sodium pentobarbital was administered intraperitoneally in doses of 4 mg. per 100 gm. of body weight, the lower abdominal aorta was cannulated, and the blood pressure was measured before and after the administration of the renal extract. Prior to the insertion of the aortic cannula the kidneys of the animals were removed and used for the preparation of renin. Subsequently the pressor effect of extracts prepared from the kidneys of the normal and treated animals was compared.

In another series of experiments, animals previously prepared by the injection of various sex hormones were similarly compared with controls as regards sensitivity to hog renin and as regards the renin content of their kidneys.

The technique used for the preparation of renin was that described by Grossman.[4]

Throughout the experiments care was taken that the controls and the treated animals should be approximately the same age and size, for Grossman and Williams[5] have shown that rats of different ages display marked variations in their response to the renal pressor substance.

Results. Since the most striking results were those obtained in adrenalectomized rats, these will be considered first.

Observations on Adrenalectomized Rats. In 7 different experiments a group of normal animals was compared with a group of rats which had been subjected to adrenalectomy 2 to 10 days previously, and subsequently treated with daily injections of 10 cc. of 0.9% sodium chloride solution. Each group consisted of from 2 to 5 animals.

* This investigation was aided by a grant from the Josiah Macy, Jr., Foundation.

In each instance the initial blood pressure of the adrenalectomized rats was lower than that of the controls, the difference varying from a few millimeters to 55 mm. In 6 of the 7 experiments the adrenalectomized animals displayed marked diminution in sensitivity to the renal extract as compared with the controls (Figure 1). In the

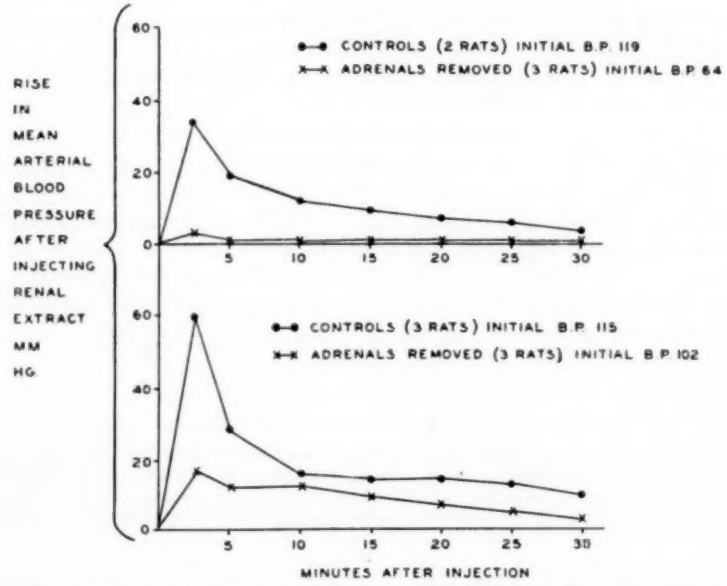

FIG. 1.—Effect of adrenalectomy on the response to the renal pressor substance. These are examples of a day's experiment. It is seen that the rats whose adrenals have been removed are very much less sensitive to renin than are the control rats. In the lower chart, the average initial blood pressure of the adrenalectomized rats is only slightly less than the normals; in the upper, it is 55 mm. less. The results are essentially the same, the renin being less active after adrenalectomy regardless of the initial blood pressure.

seventh experiment, the two groups of animals were about equally sensitive.

The findings seem at first sight to be contrary to those of Merrill, Williams and Harrison,[6] who found that removal of the adrenal glands immediately before the injection of renin did not alter the response. Accordingly, comparisons were made in the present study between rats subjected to adrenalectomy several days previously, rats from whom the glands were removed immediately prior to the injection or renin, and control animals. As shown in Figure 2, consistent differences between the two latter groups were not encountered. However, both of these groups responded to renin with a much greater rise in blood pressure than did the animals which had been deprived of adrenal tissue for several days.

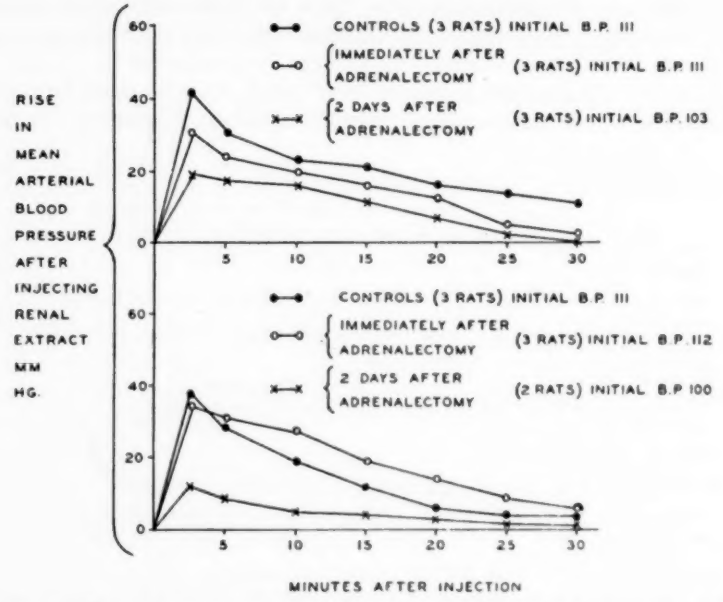
RISE IN MEAN ARTERIAL BLOOD PRESSURE AFTER INJECTING RENAL EXTRACT MM HG.
CONTROLS (3 RATS) INITIAL B.P. 111
IMMEDIATELY AFTER ADRENALECTOMY (3 RATS) INITIAL B.P. 111
2 DAYS AFTER ADRENALECTOMY (3 RATS) INITIAL B.P. 103
CONTROLS (3 RATS) INITIAL B.P. 111
IMMEDIATELY AFTER ADRENALECTOMY (3 RATS) INITIAL B.P. 112
2 DAYS AFTER ADRENALECTOMY (2 RATS) INITIAL B.P. 100
MINUTES AFTER INJECTION

FIG. 2.—Change in response to renin immediately, and 2 days after removal of the adrenal glands. In one group of experiments, immediately after removal of the adrenals, the rats are slightly more sensitive to the renal pressor substance; in the other, slightly less. Two days after adrenalectomy the rats are definitely less sensitive.

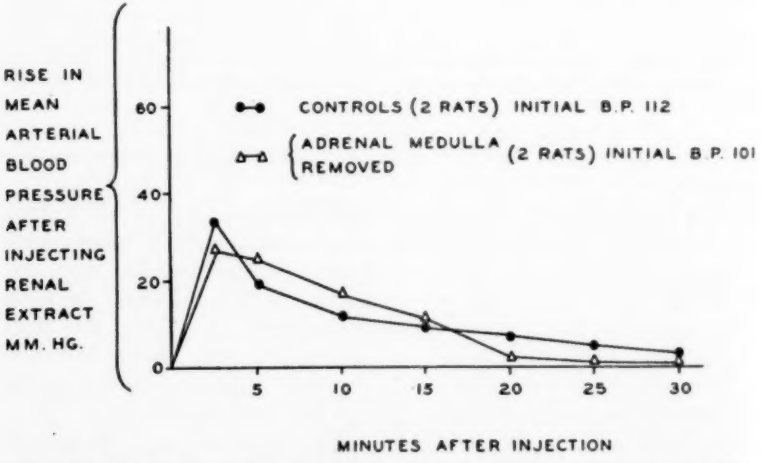
RISE IN MEAN ARTERIAL BLOOD PRESSURE AFTER INJECTING RENAL EXTRACT MM. HG.
CONTROLS (2 RATS) INITIAL B.P. 112
ADRENAL MEDULLA REMOVED (2 RATS) INITIAL B.P. 101
MINUTES AFTER INJECTION

FIG. 3.—Effect of removing the adrenal medulla on the response to renin. This shows that in rats whose adrenal medullas have been removed there is no change in sensitivity to renin.

Removal of the adrenal medulla did not alter significantly the response of rats to renin (Fig. 3).* It is apparently the adrenal cortex which is important in this regard. It might be argued that our adrenalectomized rats failed to respond to renin because such hypotensive animals were in poor general condition and would be unresponsive to any stimulus. The following facts indicate that such was not the case: 1, Some of the adrenalectomized rats had blood pressures only slightly lower than the controls and yet displayed marked diminution in sensitivity when renin was injected. 2, Hypophysectomized animals which had blood pressures as low as the adrenalectomized rats displayed a greater response than normal to the renal pressor substance. 3, In 13 adrenalectomized rats which were hyposensitive to renin, the blood pressure response to adrenalin was somewhat greater than that in the control animals. It therefore appears that the diminished sensitivity of adrenalectomized rats to the renal pressor substance is not simply due to poor general condition but represents a specific response as the result of the absence from the body of some substance formed in the adrenal cortex.

Twenty-eight comparisons between the renin content of the kidneys of normal rats and of the adrenalectomized rats were made by injecting extracts of these kidneys into normal rats. In 15 instances a greater rise in blood pressure was obtained from the extracts of the kidneys of the adrenalectomized animals. The reverse result was encountered once. Twelve comparisons gave inconclusive results.†

The observations which have been cited indicate definitely that the adrenalectomized rat is less sensitive than normal to the renal pressor substance, and that this difference is due to the absence from the body of something formed in the adrenal cortex rather than to the absence of the glands themselves. However, the kidneys of adrenalectomized rats are not deficient in the renal pressor substance.

Observations on Hypophysectomized Rats. Four groups of hypophysectomized animals were compared with normal animals of the same size and of approximately the same age, according to the technique described above, the observations being made 14 to 18 days after hypophysectomy (each group consisted of 2 to 5 rats). In one series of animals no difference was noted between the responses to renin of the treated rats and the controls. Postmortem examination revealed that hypophysectomy was incomplete in each of these

* We are indebted to Dr. Arthur Grollman, who kindly supplied us with several rats from which the adrenal medulla had been removed some weeks previously.

† We arbitrarily consider differences of less than 5 mm. as inconclusive. Apparently the kidneys of adrenalectomized animals are somewhat richer in the renal pressor substance. We do not regard this point as definitely established, however, because in preparing the extracts allowance was not made for the dehydrated condition of the kidneys of the treated animals.

animals. Three groups of animals in which hypophysectomy was found to be complete showed a markedly lower (35 to 63 mm.) average blood pressure than did the controls. In each of these instances the treated animals displayed a slightly greater initial rise in blood pressure and a considerably greater sustained elevation after injection of the renal pressor substance than did the controls (Fig. 4 *A*). Whether this difference was specifically dependent on the absence of hypophyseal tissue or was due to the lower initial blood pressure of the treated animals is uncertain.

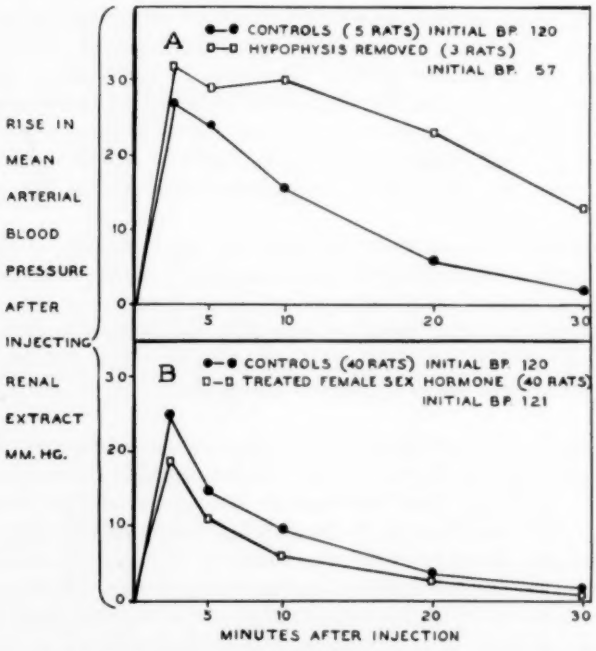

FIG. 4.—(*A*) Effect of removal of the hypophysis on the response to renin. This chart represents the averages of a day's experiments. The control blood pressures of the hypophysectomized rats are about half the pressures of the normal rats. The maximum response to renin is only slightly greater than in the controls, however their pressures remain elevated much longer. (*B*) Effect on renin response of treating rats with female sex hormones. This is the average of all the rats treated with esterin follicle-stimulating hormone and anterior pituitary-like hormone compared with their controls. The treated rats are slightly less sensitive than the controls, but the difference is small and of uncertain significance.

Twenty-two comparisons were made between the extracts of kidneys from normal rats and kidneys from hypophysectomized rats. No constant or significant difference in pressor property was

encountered, the kidneys of the normal animals having a greater effect in 5 instances, the reverse result being found 4 times, and the remaining comparisons yielding inconclusive results.

Observations on Castrated Animals. Two groups of castrated females were compared with normal females 2 and 5 weeks, respectively, after the removal of the gonads. Significant differences in the sensitivity to renin or in the amount of renin in the kidneys were not encountered. Similar negative results were obtained when a group of castrated males were compared with untreated control animals. Observations on rats which had been deprived of gonadic tissue for longer periods of time were not made.

Observations on Animals Treated With Sex Hormones. At the beginning of this study 5 female rats were on hand which had previously been treated for another purpose with injections of estrin (estradiol monobenzoate) for 2 months, followed by injections of the follicle stimulating hormone (castrate urine extract) and of the anterior pituitary-like hormone (follutein) for 5 days. It happened that control animals of the same age and size were not available at this time and these animals were compared with an equal number of older and larger controls. Marked differences were encountered between the treated and control animals. Attempts to confirm this result led to inconclusive findings. At a later date it was shown by Grossman and Williams[5] that age was an important factor in the response of rats to the renal pressor substance. Our earlier experiments on the relation of these several sex hormones to renin were therefore repeated. Five animals were studied after receiving estrin (200 rat units daily) for 1 week, followed by follicle-stimulating hormone (in daily doses equivalent to 50 cc. of castrate urine) for 5 days and then anterior pituitary-like hormone (100 rat units daily) for 5 days. A second series of animals were treated similarly except that estrin was given for 2 weeks. A third series received estrin for 3 weeks, and so on, 8 groups of animals (5 rats in each group) being treated in all. Each group of animals was compared with controls of approximately the same size and age.

The results as regards the sensitivity of the animals are summarized in Figure 4 *B*, which presents the composite curve for 40 controls and 40 treated rats. On the whole, it appeared that the animals treated with the above mentioned sex hormones were slightly less sensitive than the normal animals; but the differences were not striking and there was much overlapping in the individual animals.

Seventy-eight comparisons were made as regards the renin content of the kidneys of those animals which received injections of the sex hormones and of the normal animals. Extracts from the treated rats gave the greatest effect 14 times, the reverse was encountered 15 times, and comparisons were inconclusive 49 times. Under the con-

ditions of our experiments treatment with the several sex hormones did not seem to alter the amount of renin in the kidneys.

Two series of rats were studied after they had received for 6 days the anterior pituitary-like hormone only. These animals showed no consistent difference from the controls as regards sensitivity to renin or as regards the amount of renin in their kidneys.

Discussion. It seems that the most significant of the findings which have been presented is the marked diminution in sensitivity of adrenalectomized rats to the renal pressor substance. Whether such insensitivity is in any way concerned with the hypotension of such rats is uncertain. At the present time, there is no convincing evidence for the view that renin plays a rôle in the regulation of normal blood pressure, and the fact that removal of both kidneys does not regularly lower the blood pressure suggests that the renal pressor substance is not concerned in the maintenance of normal blood pressure. Unless one makes the assumption that a relationship exists between the amount of renin released by the kidney and the normal level of the blood pressure, one has no right to attribute the hypotension of adrenalectomized animals to their insensitivity to renin. Regardless of this question, the observations on adrenalectomized animals constitute evidence in favor of the view that renal hypertension is dependent on renin. The increased blood pressure of animals with experimental renal ischemia disappears when the ischemic kidneys are removed (Blalock and Levy[2]). The hypertension of such animals also disappears when the adrenal glands are removed (Goldblatt,[3] Page,[7] Blalock and Levy[2]). Granting the possibility that the insensitivity of adrenalectomized animals to the renal pressor substance and the insensitivity of adrenalectomized animals to the substance responsible for the hypertension produced by renal ischemia may be purely coincidental, it is simpler to explain both of these phenomena by a single assumption, namely, that the increase in blood pressure brought about by renal ischemia is dependent on an increased rate of release from the kidneys of the renal pressor substance to which adrenalectomized rats are relatively insensitive.

Our data throw no light on the cause of the striking decline in blood pressure exhibited by the hypophysectomized animals. We do not know whether such hypotension was the result of removal of the anterior or the posterior lobe, because both were removed in our experiments. Such hypotension could not be the result of decreased sensitivity to the renal pressor substance because the hypophysectomized animals were somewhat more sensitive than the controls. The amount of pressor substance in the kidneys of the hypophysectomized animals was, as nearly as could be determined by our crude methods of assay, about the same as the controls. From the

data one can assume either: (*a*) that the hypotension of hypophysectomized animals is not related to the renal pressor substance; or (*b*) that if such a relationship exists it is mediated through some unknown mechanism.

The experiments throw no light on the disputed question of the relationship between the gonads and blood pressure. The questionable slight diminution in sensitivity of animals treated with the several sex hormones might seem to support the idea that "menopausal hypertension" in women is related in some way to decreased estrin production. However, our castrated animals failed to show increased sensitivity to renin, and furthermore, the difference between the normal animals and those treated with estrin did not occur in all groups and even on the average was of only slight degree. Our data do not justify any conclusions concerning the question of a possible relationship between alterations in gonadic activity, changes in the amount or effectiveness of the renal pressor substance, and the appearance of hypertension.

Summary. A study has been made of the relationship between renin, the pressor substance present in the kidneys, and certain endocrine glands. The following results have been obtained:

1. Adrenalectomized rats kept alive with salt solution displayed decline in blood pressure and were markedly less sensitive to renin than were normal animals.

These observations afford additional evidence for the assumption that the renal pressor substance is concerned in the production of hypertension brought about by renal ischemia.

2. The kidneys of adrenalectomized rats did not contain less of the renal pressor substance than did the kidneys of normal rats.

3. Hypophysectomized rats exhibited marked lowering of the blood pressure but were somewhat more sensitive to the renal pressor substance than normal rats. Hypophysectomy did not seem to alter significantly the amount of pressor substance in the kidneys.

4. Castration did not, under the condition of our experiments, appear to alter either the amount of renin in the kidneys or the sensitivity of rats to renin. Prolonged administration of several sex hormones caused inconstant slight diminution in sensitivity to renin without changing the amount of renin in the kidneys and without altering the blood pressure.

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AN EVALUATION OF THE INFLUENCE OF OVERWEIGHT ON BLOOD PRESSURES OF HEALTHY MEN.

A Study of 3516 Individuals Applying for Periodic Health Examination.

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Among clinicians there is generally an assumption that overweight is a factor in the production of hypertension. A number of reports in the literature sustain this assumption. However, there is no general agreement as to the degree to which overweight may influence blood pressure nor has the attempt been generally made to evaluate and separate the important factor of age. It is generally conceded that, even in normal weight individuals, there is to be expected a moderate increase in blood pressure with advancing years. This is not so great as formerly assumed and most clinicians are inclined to believe that the systolic pressure should never exceed 150 mm. at any age, and that 135 mm. is more nearly the ideal in the later years of life. Two other factors which may well enter into the production of hypertension are both the degree and the duration of obesity. If obesity *per se* is indeed a factor in causing high blood pressure, it might well be expected that higher pressures will be associated with the higher degrees of overweight. Since it now appears fairly definite that duration of obesity is a factor in causing diminution of glucose tolerance,[4,5] it is possible that it also has a part in the production of increased blood pressure. It is unfortunate that these contributory factors have usually been ignored in previous studies upon this subject.

The present study concerns 2858 cases of overweight men of various ages and an attempt has been made anew to evaluate overweight as a factor in hypertension. These individuals were ambulatory, about their usual occupations, and supposedly in good health. They applied for the periodic health examination provided by insurance companies carrying their several policies. They have been unselected for the study except for the factor of overweight. In this study, 658 cases of normal weight were added for control. Those having a systolic pressure of 150 mm. or higher were considered as having systolic hypertension and those having a diastolic pressure of 90 mm. or higher as having diastolic hypertension.

The cases were distributed into weight groups as follows: a "normal" weight group of those 5% under to 5% over "ideal"

weight; and overweight groups of 6 to 15%, 16 to 25%, 26 to 40% and 41% or more above "ideal" weight. The incidence of hypertension in these various weight groups is expressed in Chart 1.

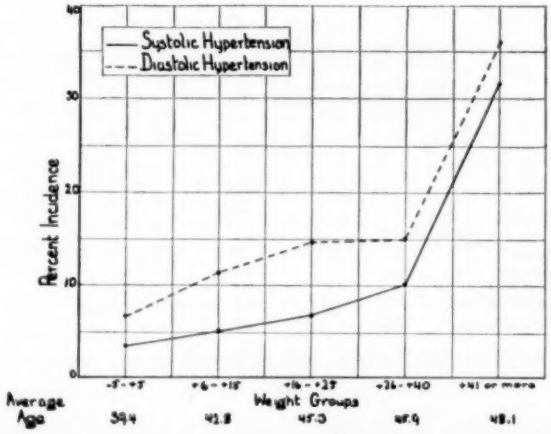

CHART 1.—Percentage incidence of systolic and diastolic hypertension in entire series of 3516 normal and overweight cases expressed in various weight groups.

For systolic blood pressure there was virtually no increased incidence among those of normal weight. There was, however, a moderately increased incidence for each overweight group up to 40%, at which point the incidence of hypertension was 10%, while in the group over 40% overweight there was a sharply increased incidence of hypertension to over 30%. The incidence of diastolic hypertension exceeded that of systolic hypertension in all ranges of overweight and, in general, showed a progressive increase to over 35% in the highest weight group.

Table 1 expresses average systolic and diastolic pressures for each of the weight groups. The systolic pressures advanced steadily from 119 mm. to 140 mm. with increasing weight. In the weight groups from 6 through 40% overweight there was little change in the average ages and an elevation of blood pressure averages from 122 to 127 mm. Average diastolic pressures generally paralleled the systolic.

TABLE 1.—AVERAGE BLOOD PRESSURES AT VARIOUS WEIGHT LEVELS.

Deviation from normal weight, %.	Average age.	Number of cases.	Systolic pressure.	Diastolic pressure.
− 5 to + 5	39.4	658	119.4	75.3
+ 6 to +15	42.8	1581	122.5	77.9
+16 to +25	45.3	915	125.0	79.7
+26 to +40	45.9	334	127.1	80.9
+41 and over	48.1	28	140.4	86.8

Chart 2 is a graphic expression of percentage incidence of systolic and diastolic hypertension for the normal weight and overweight groups taken separately in relation to age. Although there was a

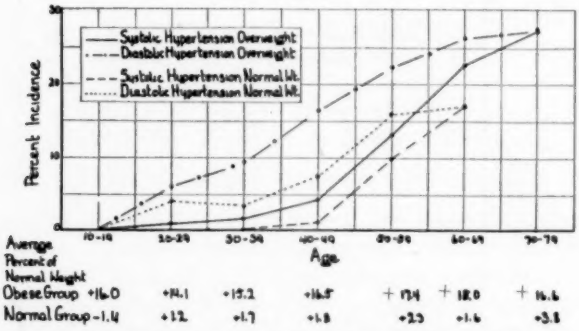
Systolic Hypertension Overweight
Diastolic Hypertension Overweight
Systolic Hypertension Normal Wt.
Diastolic Hypertension Normal Wt.
Percent Incidence
Age.
Average Percent of Normal Weight
Obese Group +16.0 +14.1 +15.2 +16.5 +17.4 +18.0 +16.6
Normal Group -1.4 +1.2 +1.7 +1.8 +2.3 +1.6 +3.8

CHART 2.—Incidence of systolic and diastolic hypertension in normal and overweight groups.

striking parallelism in the lines, it will be noted that in the incidence of both systolic and diastolic hypertension the overweight groups exceeded the normal weight groups throughout the entire age span. Among the various age groups the maximum difference in average weight for the obese group was only 4%. The striking thing about this chart is the remarkable similarity of contour of the graphs for each group and the augmenting influence of overweight on hypertension at all ages.

Table 2 presents a contrast between average systolic and diastolic blood pressures in normal weight and overweight groups for each decade from 20 through 79. In general, the average systolic pressures were higher in the overweight group. This difference was greatest in the age groups from 50 to 59, where it amounted to over

TABLE 2.—CONTRAST OF AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES AT VARIOUS AGE PERIODS BETWEEN NORMAL AND OVERWEIGHT GROUPS.

Age.	Number cases.	Average % normal weight.		Systolic pressure.		Diastolic pressure.	
		Normal weight.	Overweight.	Normal weight	Overweight.	Normal weight.	Overweight.
20–29 . .	355	+1.2	+14.1	118.0	121.1	73.5	74.4
30–39 . .	1031	+1.7	+15.2	116.6	119.4	74.0	77.2
40–49 . .	1167	+1.8	+16.5	119.0	122.1	76.3	79.1
50–59 . .	684	+2.3	+17.4	117.8	129.2	77.4	81.3
60–69 . .	233	+1.6	+18.0	131.1	134.0	80.0	83.6
70–79 . .	33	+3.8	+16.6	126.5	131.6	79.5	80.0

11 mm. In the oldest age group, the systolic pressures definitely showed a falling off which possibly can be attributed to myocardial

impairment. The diastolic blood pressure likewise averaged higher in the overweight group. Again the greatest average difference occurs in the 50 to 59 age group where it amounts to approximately 4 mm.

Comment. Huber,[2] in a study of 1332 army officers in apparently good health, found that 18% of the overweight group had systolic pressures of 140 mm. or more. This group comprised 170 cases. He concluded that underweight and hypotension were much more closely associated than overweight and hypertension.

Our results differ sharply from those of Gager[1] in the incidence of systolic blood pressures of 150 mm. and above for the various decades of life. They are similar to Gager's in the fact of a preponderance of hypertensives in the overweight group, but the percentage incidence in our study was much less. For instance, Gager found that 28.3% of his obese patients for all ages showed systolic hypertension as against our 6.5%, and 16.4% at all ages for the normal weight group as against our 2.6%. The only explanation we have for this decided difference is that his cases were selected from the Cornell Clinic and the observations presumably were made upon sick individuals whereas our study has been made upon presumably healthy individuals. It is unfortunate that Gager did not classify his patients as to the degree of overweight. Symonds[6] found an average rise of only 8 mm. for a group 50% overweight.

Overweight in this study has shown a very definite and positive influence in the production of increased incidence of hypertension. This incidence is more marked in the diastolic than in the systolic blood pressure. The study unfortunately does not contain the extreme degrees of overweight where it might be presumed that the incidence of hypertension would be even greater. Average blood pressures were consistently higher in the overweight group, but, in the cases studied, not so great as had been expected. We are inclined to agree with Mosenthal[3] that the influence of overweight on blood pressure has probably been somewhat exaggerated.

Summary and Conclusions. A study of the association of systolic and diastolic hypertension with overweight has been made on 2858 cases of healthy individuals who applied for a periodic health examination; 658 normal weight cases were used as control. The factor of age has been considered.

In this group of cases, overweight appeared to exert a positive influence in causing increased incidence of hypertension. This was more marked in the diastolic phase.

The difference in average blood pressures was greatest in the age group from 50 to 59.

The incidence of hypertension in the overweight group was generally lower than reported by other observers.

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FURTHER STUDIES ON THE TREATMENT OF CHOREA AND RHEUMATIC INFECTION BY FEVER INDUCTION.

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A study of the results by fever induction treatment used in an effort to relieve rapidly the symptom of chorea brought to light data confirming impressions gained in the management of these cases over a period of years. The origin of a number of misunderstandings that have crept into the literature seems to be explained by methods of approach in study and in the management of chorea as a whole.

This study is based entirely upon a group of cases ranging in age from 4 to 15 years. The first impression gained is the need for careful previous history even in the very young child and careful neurologic investigation before a definite diagnosis is made. The cases analyzed here postdate those reported in 1933 by Capper and Bauer[1] and all of them occurred prior to 1936. Cases seen in 1937 and 1938 are not included since their fate cannot as yet be indicated except by inference.

A diagnosis of chorea was made on 85 cases; 4 of these proved to have brain tumors, were operated upon, and the diagnosis verified; 4 had epidemic encephalitis, 7 were distinctly corpus striatum lesions with athetoid movements and were in no way related to chorea. All of these had erythrocyte sedimentation tests under 12. These 15 cases are not included in this report further but are referred to simply to show the ease with which mistaken diagnoses can be made and to call attention to the harm that might be done if fever induction therapy is used before diagnosis is certain. One hesitates to visualize what would happen to a patient with a growing brain tumor if fever induction were used instead of neurosurgery. Anyone familiar with encephalitis knows the untoward results following exposure to sunlight and heat. Careful experimentation has shown that athetoid movements of cryptogenic origin are never favorably affected by fever induction therapy.

With these subtractions we are left with 70 cases with choreiform movements for analysis and treatment. Breaking down this group of 70 their histories revealed the following:

12 had previous attacks of chorea, 9 of whom had heart lesions upon admission;
7 had multiple definite attacks of rheumatic infection including heart lesions;
5 had muscle pains without other symptoms;
1 had peritoneal irritation and epistaxis, no history of any other lesion and no cardiac involvement upon admission or discharge;
1 had joint pain admitted with a heart lesion;
18 had no previous history but a heart lesion upon admission;
16 had no previous history but had a muffling of the first sound upon admission. Seven of these were discharged from the ward with definite heart lesions. (See ultimate results later.)
10 gave no previous history of rheumatic infection, chorea, or any suggestion thereof, nor did they have heart lesions upon discharge.

Twelve of these 70 cases had palpable rheumatic nodules.

Thus in 70 cases heart involvement was clinically evident some time or other in 51; 35 were definitely damaged in earlier rheumatic episodes before attending our clinic, and 16 were involved primarily. From the standpoint of heart disease prevention we were successful up to the time of discharge in 9 of these 16 patients. Four of the remaining 7 showed no lesion after 2 years' observation, 1 of the remaining 3 had a second attack of chorea within a year with continued heart involvement, and the remaining 2 had mitral systolic murmurs with ample cardiac reserve. Therefore, of 16 cases of chorea with beginning or early heart involvement 13 completely recovered, two hearts are scarred but recovered, and but one is damaged with a recrudescence of chorea present. Of the 35 secondary cases, cardiac salvage is operating in a large proportion with encouraging results. An analysis of this at the moment would take us too far afield.

Fever induction therapy was practiced in all 70 cases. Five of these (children) were treated by a competent physiotherapist using the diathermy machine to induce fever. The patients responded quite as well from the standpoint of the amelioration of the choreiform movements as with other methods of fever induction. A greater number of children were not subjected to this treatment because they could not be controlled sufficiently well to keep them in the apparatus and adequate febrile reactions could not be obtained. This method therefore is held in reserve for older, more readily controlled patients rather than abandoned entirely.

In 65 cases, fever induction was practiced by means of typhoid paratyphoid vaccine administered intravenously as suggested by Sutton.[3]

Technique is as follows: Three and one-half hours following a light breakfast a hypodermic injection of morphine sulphate is administered, the dose depending upon the age and weight of the patient. One-half hour later an intravenous injection of 0.2 cc. of a mixed typhoid paratyphoid vaccine is given. To each cc. there are 500 million typhoid and 250 million each of paratyphoid A and B in the preparation used. Special preparations on the market with proteins removed are not as effectual as the regular stock vaccine.

The patient is wrapped snugly in blankets. An experienced nurse specials the patient and the temperature is taken at 10-minute intervals. A temperature of at least 104° F. must be obtained for the best results and remain there for 2 hours. If it tends to go over 105° F. the patient should be removed from the blankets and the temperature allowed to come down. If it does not rise to 104° F., a second intravenous injection of the same dose should be given as it descends. When the patient is out of the blankets he is ready for a hearty lunch.

Daily treatments for 8 days constitute the course for the average child. In the event that the original dose has not induced the desired temperature the dose is increased the next day 0.1 or 0.2 cc. In the exceptional case, it has been necessary to give as high as 1.5 cc. for the eighth treatment. Marked improvement is noted after the third or fourth treatment. In instances where the temperature has gone to 106° F. it has been noted after one treatment. A few have residual minor evidences after the eighth treatment which seem to clear up entirely after a week's rest.

Results. Speech improves after the third or fourth injection quite rapidly using test words such as "municipal" and "Methodist Episcopal." A permanent record of improvement is noted on the chart by the daily signature of the patient beginning on the day of admission as suggested by Gerstenberger.[2] The signature shows a decided improvement after the third or fourth injection.

A few cases are recalcitrant to the extent of needing a second and even a third series of treatments. In this group of 65 cases 5 were given 2 series and three 3 series. Eight days are permitted to elapse between series.

Two patients alone showed untoward reactions. Their temperature rose to 107° F. with extreme rapidity accompanied by evidence of collapse. Adrenalin hydrochloride 1 to 1000 in 2 to 5 m doses and an ice water enema gave prompt relief. The adrenalin hypodermic is prepared and ready for use at all times that the patient is under active treatment. There has been no evidence of any deleterious after-effects following fever induction in any of our series.

Fever induction therapy, as far as we can determine, does not influence any other manifestation of rheumatic infection. Therefore these patients must be subjected to such other antirheumatic measures as are at our command. Despite the amelioration of the outstanding symptom, chorea, we do not make the mistake of discharging these patients as cured and permitting them to assume normal activities simply because chorea has disappeared. We believe that this practice in other clinics has been followed by an increased

gravity in heart involvement and indeed perhaps heart involvement in instances where it should not have occurred. The tendency is to blame fever induction for this increase in heart damage whereas our foregoing data indicates no such thing and with improved technique our later experience convinces us that an even better record is being made in our more recent years.

The plan followed for these patients throughout the course of their illness in addition to fever induction therapy parallels our treatment of rheumatic infection excepting in the maniacal or delirious chorea upon admission. In these latter, if not controlled with phenobarbital and sodium bromide, lumbar puncture is practiced. The patients are kept at rest. We, like our English contemporaries, regard sodium salicylate as a mildly specific drug in rheumatic infection. It does seem to do more than simply relieve joint pains. The dose must be large amounting to at least 5 gm. daily accompanied by an equal or larger amount of bicarbonate of soda given in divided doses. Acetylsalicylic acid is a futile substitute. Since nausea and vomiting are due to acidosis and not irritation following the use of sodium salicylate, in addition to the bicarbonate of soda the diet employed is high in carbohydrate and low in fat. There is no trouble encountered in using these large doses.

The criteria for determining quiescence of the rheumatic attack are as follows: (1) Consistently normal temperature; (2) no cardiac dilatation or increase in pulse rate; (3) no peritoneal, muscular, or joint involvement; (4) erythrocytic sedimentation rate not faster than 12 at the end of 2 hours.

Every one of these 70 cases had undoubted rapid sedimentation rates upon admission. Careful study will reclassify supposed choreics with normal sedimentation rates in other disease groups as indicated earlier in this discussion. The sedimentation rate became normal in this group of cases in 2 instances in 1 month and in 1 in 6 months. The average is 2½ to 3 months.

All children with chorea or other rheumatic involvement are kept at rest in bed and on salicylates until all of these criteria are satisfied. Then massage followed by graduated exercise is tried, the pulse rate and temperature being the guide for increase. Iron tonics are given. Whether cardiac involvement is noted or not, this program is continued until the child shows evidence of ability to resume the normal activities of a child of its age. It is watched for evidence of decompensation, recurrence of rheumatic or choreic manifestations, and intercurrent illnesses.

We have been in the habit of giving a course of salicylates for 1 week every month for over a period of 1 year. Being cognizant of the fact that so many American observers assert that this drug is effective only in the relief of the exudative and not the proliferative lesion of rheumatic infection it is necessary to present an excuse for

this procedure. It is our contention that the drug is feebly specific in the proliferative lesion and its use in large dose both in the choreics and in the rheumatics not presenting this symptom has resulted in a greater rapidity of improvement compared with cases where it has not been used. Furthermore, the return to normal sedimentation rate has been relatively more rapid. We have also had fewer recurrences of rheumatic infection or chorea following this general plan.

Cardiac decompensation on the other hand has not occurred where this procedure has been carried out, so that we cannot dogmatically state that the use of the salicylates in themselves has been effectual or just how great a part they do play.

The whole health program sketchily outlined above plays some part in this problem of recurrence and it is impossible to say how much or how little the use of drugs or any other one element operates as a preventive measure. Suffice it that the prevention of recurrences and lessened degree of heart involvement under this régime is impressive both in chorea and in rheumatic infections without evidence of chorea.

In the light of statements made informally by other observers that there is an increased cardiac involvement in the number of choreics treated by fever induction therapy, our experience is a direct contradiction. The only inference that we can draw, as already stated, is that in the light of the rapid recovery from choreic manifestations the rheumatic background may be ignored, the child regarded as recovered prematurely, undue activities permitted too early, the child discharged before it has entered a truly quiescent stage, and it may not be adequately supervised over a long enough period to insure against secondary activation of proliferative lesions. This follow up as we have outlined it at the present moment is the essence of real heart disease prevention. Unfortunately, in our series we have a large group of children, 35 in number, whom we did not see in their primary illness, hence we were compelled to employ this method in what might be termed heart salvage which is inexplicably confused with heart disease prevention in most clinics.

Summary.—From this and our earlier series of cases of chorea we feel justified in averring that fever induction is an important and valuable addition to our therapeutic armamentarium. The danger in its use, that is, collapse and cardiac dilatation, can be eliminated by expert application of the method. True chorea in childhood is generally rheumatic in origin. Care in diagnosis will prove this. The need for antirheumatic treatment and management is necessary for a complete ultimate recovery for these patients.

The use of sodium salicylate in large doses is helpful. The erythrocyte sedimentation rate is a valuable guide in determining rheumatic activity or quiescence and is as consistent in the choreic

as in the non-choreic rheumatics. The management of the patient as a potential rheumatic in the quiescent period must be carried out over a long period of time and the methods of such management must be improved upon generally. It is hoped that the suggested plan practiced by us will prove a step in this direction.

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NOTE ON ORAL ADMINISTRATION OF POTASSIUM CHLORIDE IN THE TREATMENT OF HAY FEVER, NASAL ALLERGY, ASTHMA AND SINUSITIS.

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Benson Bloom[1] has recently reported on the oral administration of potassium salts in hay fever and asthma. He indicates that other allergic conditions may be benefited by treatment with potassium salts.

Dosage and Method of Administration. The doses for children of various ages are indicated in Table 1. The following cautions should be observed in administering the drug: Potassium chloride should be dissolved in distilled water and administered in teaspoonful doses, well diluted. It may be given in orange juice or other fruit juice before meals. *Dilution of the medication is important.* Abdominal distress and epigastric pain were not complained of when this method was followed. Syrups or other vehicles should be avoided. Potassium chloride should not be given in capsules, tablets or powder, in undiluted form. Sodium chloride intake should be limited during the period of treatment. Potassium salt is contraindicated in patients suffering from renal disease with diminution of potassium chloride excretion, or in those suffering with adrenal insufficiency. No toxic effects were noted either by Bloom or myself.

Clinical Use. The most striking results were obtained in children suffering from hay fever combined with asthma. A remarkable example was a 2-year-old child dyspneic and cyanotic, with wheezing and continuous cough. Within 12 hours after the administration of 1 grain of potassium chloride solution every 4 hours, the dyspnea, cyanosis, cough and wheezing disappeared. Satisfactory results were also obtained in patients suffering from allergic rhinitis. After 3 to 5 days' treatment with potassium chloride, the nasal mucous membrane had lost its pale, boggy appearance, the edema of the turbinates decreased and the watery nasal discharge ceased.

The cases of sinusitis observed were either chronic or followed acute upper respiratory infections. In several patients suffering

TABLE 1.—RESULTS OF USE OF POTASSIUM CHLORIDE IN ALLERGIC STATES.*

Name.	Age (years).	Date, 1938.	Dosage, grains t.i.d.	Results.
(A) Hay Fever Without Asthma.				
F. A. (sister of J. A.)	18	10–30	5	Hay fever improved within 48 hrs.
Mrs. A.	..	10–30	5	Sneezing and eye symptoms greatly diminished within 72 hrs.
Mrs. J. A.	..	10–21	5	No sneezing or nasal congestion after 24 hrs.
Mrs. S. (Mother of H. S. and N. S. under Hay Fever With Asthma.)	..	10–25	5	Sneezing, nasal congestion greatly diminished after 24 hrs.
(B) Hay Fever With Asthma.				
J. D.	5	10–20	2½	Stopped wheezing within 48 hrs.
P. P.	6	10–21	2	Refused to take in water. Wheezing relieved when given in orange juice.
J. U.	5	10–24	3	Severe wheezing with dyspnea. Marked improvement in 24 hrs. Wheezing disappeared in 48 hrs.
N. S.	4	10–25	1½	Refused to take in plain water. Dissolved in orange juice. Wheezing disappeared and symptoms cleared in 24 hrs.
H. S.	7	10–25	3	Same as above.
M A.	2	10–31	1	Severe exudative diathesis, eczema and asthma. Wheezing stopped after 24 hrs. Previously difficult to control with adrenalin and ephedrin.
J. A.	14	10–30	4	Wheezing decreased within 48 hrs.
B. H.	10	11–5	4	Severe asthma. Greatly improved in 24 hrs. Wheezing stopped in 48 hrs. Has always been difficult to control with adrenalin and ephedrin.
R. D.	10	11–9	4	Wheezing stopped in 48 hrs.
(C) Allergic Rhinitis.				
M. W.	8	11–7	3	Pallor and turgescence of mucous membrane disappeared after 4 days.
R. D.	10	11–9	4	Excessive nasal secretion diminished within 3 days.
M. K.	10	11–11	4	Nasal obstruction and secretion cleared after third day.
M. K., Jr.	7	11–15	3	Mucous membranes pink and edema disappeared after 5 days.
E. W.	3	11–14	2½	Relieved of nasal obstruction after 48 hrs.
G. D.	8	12–15	3	Also had slight wheeze which cleared within 48 hrs.
(D) Sinusitis.				
M. P.	6	10–21	2½	Roentgen ray showed definite cloudiness over maxillary sinus. Relieved of nasal congestion after 72 hrs.
A. F. A.	..	10–20	5	Maxillary sinus tenderness. Relieved after 48 hrs.
Mrs. M.	..	10–22	5	Chronic sinusitis. Relieved after 48 hrs.
W. G.	..	10–23	4	Chronic sinusitis with nasal polyps. Relieved.
J. L.	13	11–15	4	Subacute sinusitis aggravated by use of argyrol. Congestion relieved after 24 hrs.
J. H.	12	12–1	4	Chronic sinusitis for over 1 mo. Relieved after 48 hrs.
F. A.	8	12–1	4	Improved after 48 hrs.
M. K.	6	12–15	3	Relieved of chronic catarrhal nasal congestion with tenderness over maxillary sinuses.

* Results of any hay fever treatment begun no earlier than October 21 are useless in evaluating that treatment.—EDITOR.

from sinusitis, the alleviation of the maxillary tenderness and of nasal fulness and discomfort was striking, after the administration of potassium chloride. The nasal discharge became thinner and less tenacious in character after several days' treatment with potassium chloride. Allergy probably is a factor in some cases of sinusitis.

The alleviation of symptoms of hay fever with asthma, allergic rhinitis and sinusitis here reported was striking.

The exact pharmacologic mechanism is not clear, though Bloom thinks the clinical effect depends on the potassium ion of the salt. Stoesser and Cook[2] have shown that diminished sodium chloride intake in asthmatic children decreased symptoms, while addition of sodium chloride during a period of remission caused the symptoms to reappear. These authors conclude that, "asthma may be aggravated by sodium chloride and mitigated by depletion of body salts, even in the presence of excessive hydration."

In the series of cases here reported, no determinations were made of the sodium or potassium content of the blood or of the excretion of these elements in the urine. However, a mild diuresis occurred following administration of potassium chloride to several of the patients here noted. Perhaps the action of the potassium ion is a displacement of the sodium ion in the tissues, which produces a local tissue dehydration. This may explain the decrease in turgidity of the nasal mucous membrane in allergic rhinitis, and may account for the relief and improved drainage obtained in sinusitis. The exact pharmacologic action of the potassium ion in these conditions deserves further intensive study.

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LYMPHOGRANULOMA VENEREUM: TREATMENT OF 300 CASES.

WITH SPECIAL REFERENCE TO THE USE OF FREI ANTIGEN INTRAVENOUSLY.

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THE treatment of lymphogranuloma venereum has received only scant consideration in the literature up to the present time. Each of the several clinical entities now embraced by this disease has various forms of therapy described for its individual cure or palliation. When

lesions such as local adenopathies, generalized adenopathies and rectal conditions were coördinated into one disease picture, attempts were made to use a single agent for the cure of all manifestations. Thus, Hellerstrom,[9] recognizing the systemic nature of this disease, used the Frei antigen intravenously as early as 1931 in one case. Among others, chemical agents such as tartar emetic, fuadin, gold salts, emetine and the arsenicals, were tried. Foreign protein therapy, Roentgen ray therapy, and attempts at immunization with Frei antigen have been used with varying degrees of success. Systemic manifestations of the disease have been stressed and clinically described by Eberhard[2] and Gutman.[7] To combat these is of primary importance in an effort to arrest the disease process wherever it may manifest itself in the body. The adjuvant methods, radical surgical or local conservative, are then likely to become useful and effective.

This report deals with the treatment of 300 consecutive cases of lymphogranuloma venereum. A group (207) of this series received Frei antigen intravenously, while the remainder (93) received the various types of therapy suggested by other authors.

Frei Antigen Therapy. Frei antigen was used intracutaneously in the treatment of lymphogranuloma in 1927 by Gay Prieto.[5] The fact that amelioration of symptoms occurred when the skin test was performed led to the use of this method. A report of treatment of 200 cases by Wien and Perlstein[16] represents the largest single series of cases among whom this type of treatment was used. The results reported are encouraging. This method, however, has its objection in that a positive intracutaneous reaction occurs with each successive injection. It was not found possible to alter the Frei reaction from positive to negative even after a series of 60 to 70 injections. This fact has been confirmed repeatedly.

The intravenous route offers a faster, more effective and less objectionable way of using this form of treatment. Frei antigen intravenously has been used in this group of cases since 1934, and about 3500 intravenous injections have been given to 207 patients to date. With the exception of a small number confined to the hospital the treatment was given to ambulatory patients. A routine method was found sufficient and effective in all cases. This consisted of the intravenous injection of 0.3 cc. of Frei antigen 3 times a week on alternate days. There were no untoward alarming symptoms due to therapy in any case. No embolic phenomena were observed, in spite of the fact that free particles could be seen in the fluid used intravenously.

Type of Antigen. The sources of human antigen are uncontaminated suppurative buboes which have not broken through the skin. Aspirated material can be used filtered or unfiltered after the usual preparation, suggested by Frei.[4a] The human unfiltered antigen was used throughout the entire group for both diagnosis and therapy.

Reactions After Intravenous Treatment. As a rule, only the first and second injections of the Frei antigen produce definite symptoms. These are a chill, fever, malaise, occipital headaches, occasionally nausea and vomiting; infrequently a generalized maculo-erythematous rash which fades in 48 hours; and in some cases joint pains. The succeeding injections produce only headaches and malaise, but are therapeutically as effective as the initial doses, despite the lack of a severe systemic reaction. The initial intravenous injection into 12 patients unaffected by lymphogranuloma produced no reaction whatever.

With some modifications the experience of the author is very similar to that of Gay Prieto and Egea Bueno.[5] Four main types of reaction may take place after the initial injection (Fig. 1): *A*, the prompt reaction; *B*, the delayed reaction; *C*, the delayed protracted; and *D*, no reaction, "anergic reaction." A fifth type, a successive repeated reaction, is very unusual.

A prompt reaction (*Chart A*) occurs in 2% of the cases. It begins about ½ to 1 hour after the injection. The patient gets a severe chill which may last from 20 minutes to 4 hours. This is associated with marked perspiration and prompt rise in temperature to 103° or 104° F. In one case the temperature rose to 106° F. The temperature subsides within a period of 24 hours. During this time the patient complains of occipital headaches which may persist for from 18 to 36 hours. Occasionally there is nausea and vomiting. Focal reactions take place: the inguinal glands when enlarged become more tense, fluctuant inguinal abscesses occasionally break open and discharge profusely, and the pain in the inguinal swellings becomes more pronounced at the height of the reaction. Within 24 hours all of these manifestations subside to a remarkable degree, the swelling recedes and the local pain stops. Patients with rectal or genital involvement report a distinct change in symptoms. The purulent and bloody discharge becomes less. The local pain and tenderness practically disappear. Local examination, however, reveals little anatomic improvement. The constitutional symptoms likewise show a marked improvement. The feeling of malaise, headache, and muscle pains, occasionally joint pains promptly subside.

A delayed reaction (*Chart B*) is the most common, occurring in about 68% of cases. It begins about 10 to 12 hours after the injection and lasts for 12 to 24 hours. The reaction is identical with that described above for the immediate reaction, with the exception of the difference in the later time of onset. The fever and constitutional reactions subside at the end of a 24-hour period.

A delayed protracted reaction (*Chart C*) is observed in 4% of the cases. The patient feels no untoward effects for about 24 hours after injection. The reaction then commences with a severe chill which may last for ½ to 2 hours and is accompanied by a fever up

to 106° F. These symptoms will not subside completely until the end of the fifth day after the initial injection.

Anergic reaction (*Chart D*). This type of reaction occurs in about 25% of the cases seen. The patient is entirely unaffected by the injection of the Frei antigen from the very beginning.

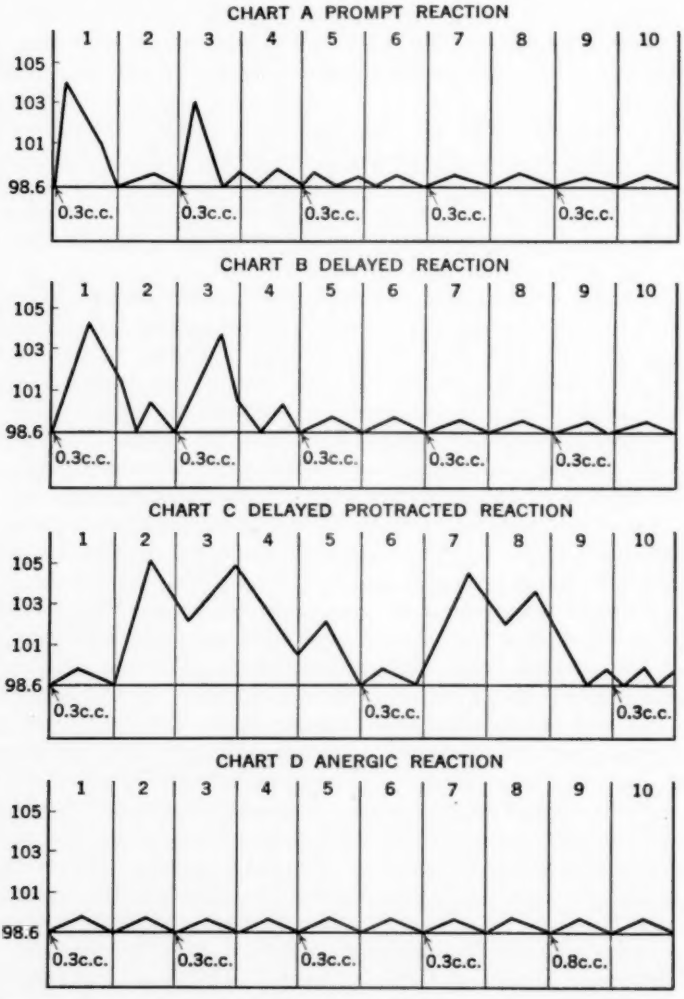

FIG. 1.—Types of fever curves following the intravenous use of Frei antigen.

In two of our patients a severe reaction of the delayed protracted type occurred each time the Frei antigen was given intravenously. Fortunately, this type of reaction is very unusual.

When the *second dose of antigen* is administered, after 48 hours, the chill, fever, and headache, repeat themselves in a manner similar to that after the initial injection. The reaction is, however, not as violent.

A change of antigen in the course of treatment may or may not produce a repetition of the initial reaction. The potency of the new antigen used and the extent of the patient's disease come into consideration when a new antigen is substituted.

Results of Treatment. For purposes of discussion, our cases may be divided into three groups: those with glandular, those with rectal, and those with genital lesions (Tables 1 and 1*A*). It must be remembered that lymphogranuloma venereum is venereal in origin and that a patient having this disease may also be suffering from one or more of the other known venereal diseases. Thus, only about one-half of our series showed uncomplicated lesions due to lymphogranuloma alone, while the remainder showed two or more coëxisting diseases (Table 2). Treatment of the primary lesions, which usually are in the form of small ulcerations on the genitalia or a urethritis, is negligible, since the lesions (commonly overlooked) heal invariably of themselves within a period of 2 weeks.

TABLE 1.—LYMPHOGRANULOMA VENEREUM. CLASSIFICATION.*

	Grand total.	Male.			Female.		
		Total.	Wh.	Col.	Total.	Wh.	Col.
Glandular	186	172	66 (11)	106	14	1	13
Rectal	55	23	23 (3)	0	32	12 (9)	20
Genital	59	33	3	30	26	2 (2)	24
Total	300	228	92 (14)	136	72	15 (11)	57

* The figures in parentheses refer to natives of Puerto Rico.

TABLE 1*A*.—LYMPHOGRANULOMA VENEREUM. RACE.*

	Total.	%.
White	107 (25)	35 (8)
Colored	193	65
Total	300	100

* Figures in parentheses refer to natives of Puerto Rico.

TABLE 2.—LYMPHOGRANULOMA VENEREUM. CASES ASSOCIATED WITH OTHER VENEREAL DISEASES.

Diseases.	Total No.	Cases with 1, 2, 3 and 4 diseases.	%.
Lymphogranuloma	157	157	52.3
Lymphogranuloma and syphilis	71	99	33
Lymphogranuloma and gonorrhea	26		
Lymphogranuloma and chancroid	2		
Lymphogranuloma, syphilis and gonorrhea	35	42	14
Lymphogranuloma, syphilis and chancroid	6		
Lymphogranuloma, gonorrhea and chancroid	1		
Lymphogranuloma, syphilis, gonorrhea and chancroid	2	2	0.7
Total	300	300	100

CASES WITH GLANDULAR LESIONS. This group includes those having inguinal, femoral and pelvic adenopathies. Of 186 cases, 111 (60%) subsided without abscess formation (Table 3); and 75 (40%)

TABLE 3.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 111 CASES WITH NON-SUPPURATIVE ADENOPATHY.

Classification.	No. of cases.	Sex.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Av. No. of inj.	Results.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
								Excellent.	Good.	Poor.			
A. Inguinal unilateral	40	M	28	6 wks.	Frei antigen 29 Excision 4 None 7	7 wks. 6 mos. 8 mos.	8	27	2 4 7	.. .. ..	12	7	2
B. Inguinal bilateral	21	M	30	6 wks.	Frei antigen 12 Excision 2 None 7	6 wks. 6 mos. 8 mos.	8	11	.. 2 7	1	9	6	
C. Inguinal unilateral with penile primary	15	M	33	4 wks.	Frei antigen 14 Excision 1	4 wks. 4 mos.	7 ..	10 ..	3 ..	1 1	5	3	2
D. Inguinal bilateral with penile primary	12	M	26	6 wks.	Frei antigen 10 None 2	6 wks. Unkn.	11 ..	8 Unknown	..	2	8	7	
E. Inguinal bilateral with urethritis	4	M	28	6 wks.	Frei antigen 3 Excision 1	8 wks. 4 mos.	16 ..	1 ..	2 1				
F. Inguinal bilateral with vulval primary	10	F	26	4 wks.	Frei antigen 6 None 4	4 wks. Unkn.	6 ..	6 4	.. ..	.. ..	4	3	
G. Inguinal bilateral with bubonuli	3	M	28	4 wks.	Frei antigen 2 Tartar emetic 1	4 wks. 3 mos.	11 10	2 ..	.. ..	.. 1	1		
H. Generalized simulating infectious mononucleosis	3	M	28	3 wks.	Frei antigen 2 Incision 1	6 mos. 5 mos.	15 ..	1 ..	1 ..	.. 1	1	1	
I. Inguinal with granuloma symphesis pubis	2	M	23	1½ yrs.	Frei antigen 2	8 wks.	16	1	1	..	1		
J. Generalized with primary lesion on finger	1	M	16	3 wks.	Excision 1	3 mos.	..	..	1				

went on to suppuration (Table 4). This percentage is definitely less than the usual 60% suppuration reported by most authors. Early diagnosis and prompt therapy undoubtedly contributed to this reduction. The deep inguinal and pelvic adenopathies offered no difficulties since all of them subsided without suppuration. No case of generalized peritonitis from suppurative pelvic adenopathy has thus far been reported. The type of therapy and comparative results in the treatment of the suppurative and non-suppurative groups are recorded in Tables A and B.

The term "healed" refers to absence of constitutional symptoms, and disappearance of clinical signs of actual disease in a period of average optional duration of treatment, that is, 6 weeks in the inguinal group treated with Frei antigen. The term "good result" implies healing in a period of about 3 months without resort to any other

therapeutic measure. Poor results are used to denote cases which required longer than 3 months for healing.

TABLE A.—NON-SUPPURATIVE ADENOPATHIES—111 CASES.

	No. of cases.	Duration of symptoms (wks.).	No. of injections.	Results.		
				Healed.	Good.	Poor.
Frei antigen	81	6	9	68	9	4
Excision	10	24	..	..	8	2
Tartar emetic	1	12	..	..	..	1
No treatment	19	32	..	..	17	2

TABLE B.—SUPPURATIVE ADENOPATHIES—75 CASES.

	No. of cases.	Duration of symptoms (wks.).	Duration of treatment (wks.).	No. of injections.	Results.		
					Healed.	Good.	Poor.
Frei antigen	62	9	8	11	51	8	3
Excision	2	5	12	..	1	1	
Incision and drainage	9	9	20	..	1	1	7
Tartar emetic	1	5	4	..	..	..	1
None	1	5	?	..	..	1	

Cases receiving Frei antigen intravenously showed the best results, as 119 of 143 healed in 6 weeks (83%) with or without suppuration and sinus formation. To this group may be added 17 cases (12%) which took 3 months to heal. A very significant fact is that over a period of 2 years it was not found necessary to incise and drain or excise a single case of suppurative or non-suppurative adenitis observed. Aspirations, where indicated, and Frei antigen intravenously were found adequate. These results compare exceedingly favorably with those of Prehn[14] who reports that incision was done in about 75% of his cases, necessitating hospitalization of from 6 to 38 weeks.

Thus, it may be stated that when no treatment was instituted, about 25% of cases healed spontaneously within the period of 6 weeks which was the average optimal time of any therapy used. When any method mentioned above was used all of the cases had healed at the end of 8 months of observation in a series of 60 cases.[10a] Excision of all diseased tissue is often impossible. In about one-third of the cases, retroperitoneal enlargement accompanies the evident inguinal adenopathy. The fact that elephantiasis of the genitalia may take place after a complete removal of the inguinal nodes also militates against this procedure. However, in 12 cases of block excision an average of 5 months' observation and treatment was

necessary and the results were good in 10 of the 12 cases. There was no evidence of genital elephantiasis in this group when followed up.

TABLE 4.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 75 CASES WITH SUPPURATIVE ADENOPATHY.

Classification.	No. of cases.	Sex.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Av. No. of inj.	Result.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
								Excellent.	Good.	Poor.			
A. Inguinal unilateral	6	M	37	5 wks.	Frei antigen 5 None 1	4 wks. Unkn.	9 ..	3 ..	2 1	.. ..	1	1	
B. Inguinal bilateral	7	M	27	4 wks.	Frei antigen 7	7 wks.	15	6	1	..	1	2	
C. Inguinal unilateral with penile primary	9	M	27	5 wks.	Frei antigen 6 Excision 3	6 wks. 5 mos.	9 ..	4 1	2 1	.. 1	1	1	
D. Inguinal bilateral with penile primary	4	M	28	1½ yrs.	Frei antigen 2 Incision 2	4 wks. Unkn.	7 ..	2 ..	.. 2	.. ..	2		
E. Inguinal unilateral with spontaneous sinus	22	M	29	5 mos.	Frei antigen 19 Incision 3	7 wks. 4 mos.	11 ..	19 ..	.. 3	.. ..	7	6	1
F. Inguinal bilateral with spontaneous sinus	5	M	28	6 mos.	Frei antigen 3 Incision 2	3 wks. Unkn.	7 ..	3 ..	.. ..	.. ..	2	1	
G. Inguinal unilateral with sinus and penile primary	4	M	35	6 wks.	Frei antigen 4	17 wks.	16	..	4	..	1	2	
H. Inguinal bilateral with sinus and penile primary	10	M	31	5 wks.	Frei antigen 8 Tartar emetic 1 Incision 1	3½ mos. 1 mo. 3 mos.	25	5	.. .. ..	3 1 ..	6	6	1
I. Inguinal bilateral with urethritis	4	M	23	3 wks.	Frei antigen 4	7 wks.	14	4	..	..	2	2	
J. Inguinal bilateral with vulval primary	4	F	28	3 mos.	Frei antigen 4	8 wks.	8	4	..	..	2		

Until recently the treatment of the inguinal lesions presented a surgical problem. At present, it may be stated that the problem is that of treating a systemic condition with local manifestations and that conservative methods are by far the most commendable in this group. The treatment recommended is the use of Frei antigen intravenously with aspiration of local suppurative foci where indicated.

CASES WITH RECTAL LESIONS. The natural course of the rectal lesions is one that leads to chronicity. The average duration of the disease at the time of examination is about 3 years. The various manifestations may be seen in Tables 5 and 6. It is noteworthy that among the 23 males, the largest group, 12 (52%), was due to pederasty. This group represents cases with primary implantation of the disease in the rectal wall. There is, however, ample proof that the rectal lesions may develop as a result of previous primary genital lesions and a secondary spread to the pelvic lymphatics by direct extension through the femoral and inguinal canals.[10b] The rectal lesions were tubular in type in 32 out of 55 cases (58%). This tubular group represents persistent subacute and chronic lesions,

while the diaphragmatic type, 23 cases (42%), represents more of the healed type of fibrous stricture.

TABLE 5.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 23 MALES WITH RECTAL LESIONS.

Classification.	No. of cases	Average age.	Type. Tub.	Type. Dia.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Results. Excellent.	Results. Good.	Results. Poor.	Pos. Wass.	Pos. G. C.	Pos. Duerey.
A. Chronic proctitis, rectal stricture due to pederasty	12	43	9	3	5 yrs.	Frei antigen 11 Dilatation 2	18 wks. 18 wks.	19 ..	.. ..	3 2	7 ..	6	2	
B. Chronic stricture, secondary type, previous inguinal adenopathy	6	42	6	..	1 yr.	Frei antigen 4 Dilatation 1 Tannic acid 1 Tartar emetic 1 Operative 1	30 wks. 30 wks. 30 wks. 30 wks. 30 wks.	26	.. ..	2 .. 1 .. 1	2 1 .. 1 ..	2	1	
C. Acute proctitis, secondary type, previous inguinal adenopathy	2	49	2	..	8 mos.	Frei antigen 2 Fuadin 1	64 wks.	23 ..	.. ..	.. ..	2 1			
D. Ulcerative sigmoiditis	2	39	2	..	1½ yrs.	Tartar emetic 1 Emetine } 1 Carbarsone }	4 wks.	..	..	..	2	1	1	
E. Condyloma, fistulas in ano	1	33	..	..	1 yr.	Incision 1	3 wks.	..	..	..	1			

TABLE 6.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 32 FEMALES WITH RECTAL LESIONS.

Classification.	No. of cases.	Average age.	Type. Tub.	Type. Dia.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Result. Excellent.	Result. Good.	Result. Poor.	Pos. Wass.	Pos. G. C.	Pos. Duerey.
A. Rectal stricture	17	30	8	9	3 yrs.	Frei antigen 2 Resection 2 Non-sp. prot. 1 Colostomy-dil. 2 Dilatation 2 Operative 2 None 5 Tartar emetic 1	2 yrs.	20	.. ..	.. 1 .. .. 2	2 1* 1 .. .. 2 5 1	4	1	
B. Rectal stricture with rectovaginal fistulas	5	36	2	3	10 yrs.	Non-sp. prot. 1 Dilatation 1 Frei antigen 1 None 2	8 wks. 2 yrs. 8 wks. 2 yrs.	.. .. 16 ..	.. ..	.. ..	1 1 1 1* 1†	1	1	
C. Rectal stricture, pelvic exudate	1	34	..	1	Unkn.	Roentgen ray 1	....	..	..	1				
D. Rectal stricture, inguinal adenopathy	2	29	1	1	3 yrs.	Dilatation 2	Unkn.	..	..	1	..	1		
E. Acute and chronic proctitis	1	26	1	..	9 yrs.	Frei antigen 1	40 wks.	24	..	..	1	1		
F. Peri-anal excoriations	2	27	..	..	5 mos.	Frei antigen 2	12 wks.	13	..	2	..	2		
G. Fistulas in ano	3	23	..	..	6 mos.	Frei antigen 3	Unkn.							
H. Rectal stricture, primary infection	1	11	1	..	4 yrs.	Frei antigen 1	2 yrs.	40	..	..	1			

* Fatal. † Poor.

The tabulation of the type of treatment and results obtained shows the comparative efficacy of the procedures used thus far. The totals for the group show good results in 17 and poor results in 38 cases. Surprisingly enough, no cases could be considered completely healed. The reason for this will become more evident when all procedures used are considered separately (Table C).

TABLE C.—RECTAL CASES—MALE 23 AND FEMALE 32—TOTAL 55.

Type of treatment.	No. of cases.	Duration of disease (yrs.).	Duration of treatment.	No. of injections.	Results.		
					Healed.	Good.	Poor.
Frei antigen	25	4	1 yr.	23	..	7	18
Non-specific protein therapy	2	3	1 yr.	..	..	..	2
Tartar emetic	5	4	7 mos.	..	..	..	5
Roentgen ray therapy	1	4	3 wks.	..	..	..	1
Dilatation	9	5	1 yr.	..	..	8	1
Colostomy and dilatation	2	6	1 yr.	..	..	2	
Mobilization of rectum with excision of scar	3	3	4 yrs.	..	..	..	3
Resection	2	3	2 yrs.	..	..	..	2
Incision of fistulas	1	1	3 wks.	..	..	..	1
No treatment	5	4	3 yrs.	..	..	..	5

The intravenous use of Frei antigen alone has yielded surprisingly good symptomatic relief. The patients lose their constitutional symptoms and lose most of their rectal pain. This occurs as early as after the second injection. The disease process, however, appears for the most part anatomically unchanged. It must be observed that the treatment is continued over a period of many months or years. For a variable period (2 to 3 months) after the administration of Frei antigen no appreciable change will be seen. However, after this period evidence of slow regression will become apparent. Epithelization of ulcerated surfaces, beginning fibrosis and a subsidence of the acute and chronic inflammation will now ensue. In the group so treated there was certainly no progression of the disease process. It is the writer's impression that the effect of the antigen is definitely beneficial, even if not curative. The good results obtained are thus mainly functional and not anatomic. When administered to patients having fibrotic changes, the Frei antigen shows no evident effect. The fibrosis represents an end stage of the local process, and therefore is not likely to be affected by the antigen. It must be remembered, however, that acute and subacute pathologic lesions have been demonstrated in the pelvic lymph nodes in cases of fibrous stricture as long as 12 years after the onset of the lesion. It would seem advisable, therefore, that even these cases be given Frei antigen in an effort to cause these foci to subside. A course of at least 6 weeks' treatment similar to the treatment for inguinal bubo seems advisable before mechanical measures are resorted to.

The use of tartar emetic, Roentgen rays and non-specific protein therapy have all proved of no avail.

Rectal dilatation alone was found of definite benefit in those cases where actual disease had completely subsided. A surprisingly small lumen will leave the patient asymptomatic. Dilatation alone is contraindicated in the presence of active proctitis or pelvic inflammation. It is associated with severe local pain and marked systemic reactions. Mathewson[12] particularly recommends dilatation. He believes colostomy need not be resorted to, since 87 of his 89 cases with obstructive stenosis were relieved by dilatation alone. In the writer's series, dilatation alone was extremely effectual when the above-mentioned indications presented themselves. Of 9 cases, 8 yielded good functional results.

Colostomy may, at times, become an emergency procedure. In case of partial obstruction, colostomy may be optional. However, colostomy may be delayed or possibly avoided by the use of intestinal intubation for abdominal decompression described by Abbott and Johnston.[1] After the distention is relieved, sufficient time may be taken for a thorough investigation of the case and the most suitable course followed. As a rule, colostomy should be seriously considered in cases with fulminating lesions which do not react to palliative measures or to attempts at immunization with Frei antigen. Cleansing of the distal loop and rest have proved very useful and permitted a later closure in some cases. The suggestion of Lockhart-Mummery for the treatment of fibrous stricture of the rectum may well be followed as a general principle. "To ascertain the type and extent of the stricture, it is advisable to examine even with partial dilation, so that the upper limits can be explored and the condition of the proximal bowel immediately above verified. Sigmoidoscopy may thus be performed under anesthesia if necessary. This should be done with great care, and splitting of the rectal wall when inflammation is present should be avoided. In suitable cases the stricture is dilated and treated by continual cleansing. Results of subsequent dilatation are excellent and permanent, if the patient will endure the inconvenience of dilating long enough to counteract the contraction of scar tissue."

Hayes,[8] reporting 160 cases of rectal stricture, found colostomy a necessary procedure in 31 cases. When these cases were followed up, he found it possible to close the colostomy in only one of the operated cases. He was undoubtedly dealing with the tubular proliferative type of rectal stricture.

Colostomy and dilatation thus play an important rôle in the treatment. The surgical risk is very small as compared with the following procedures recommended by other authors.

Mobilization of the Rectum and Excision of the Perirectal Scar Tissue. This procedure wherever done was attended with a failure

and recurrence. It results in stirring up of latent foci in the endopelvic fascia and eventually produces more fibrosis, creating a condition much worse than that for which the procedure was undertaken. The object of the operation is to release the supposedly disease-free rectal wall. Since the rectal wall itself is always involved, the rationale for the procedure is faulty. Good results were reported in 2 cases by Gomez-Duran[6] with this procedure upon old healed strictures of the ring type. However, in this type of lesion the procedure is unnecessary, since dilatation alone is sufficient.

Resection of the Rectum. A review of the procedure of radical resection for lymphogranuloma venereum shows a series of disastrous and unsatisfactory results from every point of view. Thus, Frei[4b] reviewed 105 cases of various types of rectal amputations with a follow-up of 90% unsuccessful results.

Peterson[13] quotes Anschuetz as having a mortality rate of 39% among 13 cases resected. The remaining cases showed poor follow-up results. Only those with colostomies did comparatively well. Radice[15] likewise reported 16 cases with 7 resections with poor results. The resulting complications of perineal fistulas, recto-vaginal fistulas and permanent incontinence were attributable to persistence of a low grade infection. The reasons for failure are evident when the procedure is attempted. The mobilization of the diseased rectum is extremely difficult. The normal anatomic planes of cleavage are entirely obliterated and replaced by inflammatory scar tissue. The mesosigmoid likewise becomes shortened by the extension of the inflammation from below. This most often prevents an adequate mobilization for use in anastomosis. Preservation of the sphincter ani is a practical impossibility in most cases because the perianal tissue is most often itself involved.

A very important consideration that accounts for the failure and high mortality in resection is the fact that as long as there remains any evidence of activity of the disease one must assume that a phlegmonous type of inflammation is still present in the endopelvic fascia. Attempt at dissection in such tissue is analogous to incision of a phlegmon elsewhere and there is a definite risk of a lymphatic spread of the disease.

Incision or Excision of Fistulous Tracts. The repair of recto-vaginal fistulas or excision of rectal fistulas has proved unsatisfactory as long as any disease remained active in the rectum itself. Recurrences have resulted invariably.[3] Before this type of surgery is attempted the disease process itself must be cleared up more or less completely.

Palliative Procedures. Palliative methods such as rest in bed, low-residue, high-vitamin diet, retention enemata of olive oil or cotton seed oil, rectal irrigations with 2% tannic acid, and solutions of quinine bisulphate, 1 : 4000, have been used with benefit to the patient.

From the foregoing one may reasonably conclude that radical surgical procedures alone or palliative methods alone are inadequate. A rational combination of both palliative procedures and the more conservative surgical methods seems the most advisable course to take at present in the treatment of the rectal lesions.

Cases With Persistent Genital Lesions. A total of 59 cases of this type were observed, 26 females and 33 males. The average duration of the lesions was over 2 years. Among the females, the lesions ranged from periurethral granulomata with esthiomene to the various ulcerations of the genitalia or their resulting fibrosis (Table 7). In the males, the lesions were represented by chronic ulcerations of the penis (Table 8).

Table 7.—Lymphogranuloma Venereum: Clinical Data of 26 Females With Genital Lesions.

Classification.	No. of cases.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Result.			Pos. Was.	Pos. G. C.	Pos. Ducrey.
							Excellent.	Good.	Poor.			
A. Periurethral granuloma with esthiomene	7	28	3 yrs.	Frei antigen 7 Tartar emetic 1	8 mos.	32	2	3	..	3		
B. Ulcerations of labia minora with esthiomene	5	28	2 yrs.	Frei antigen 5	8 mos.	33	2	..	1	4		
C. Stenosis of vaginal introitus	3	32	1½ yrs.	Frei antigen 3	6 mos.	29	..	3	..	2		
D. Fourchette: chronic ulceration	3	32	1½ yrs.	Frei antigen 3	5 mos.	10	..	..	3	2		
E. Chronic cervical erosion	2	36	Unkn.	None	....	..	..	..	2			
F. Ulceration of perineum	1	36	Unkn.	Frei antigen 1	1 wk.	3	..	..	1	1		
G. Chronic hypertrophic ulceration of vulva	1	36	9 yrs.	Frei antigen 1	4 wks.	22	..	..	1			
H. Ulceration of vaginal wall	1	24	Unkn.	None	....	..	..	..	..	1		
I. Esthiomene	1	27	2 yrs.	Frei antigen 1	5 mos.	22	..	..	1			
J. Esthiomene with rectovaginal fistula	1	26	3 wks.	None	....	..	..	..	1			

Treatment with Frei antigen alone was effectual in 24 of 39 cases (60%). Other methods such as tartar emetic, cauterization, or operative measures, yielded good results in 2 out of 7 cases (28%). In 13 cases no treatment was used and poor results were uniform. The lesions progressed.

The largest single subdivision among the females is that of periurethral granulomata with esthiomene (12 cases). These periurethral lesions lead to obstruction of the urinary flow and thus produce uremic symptoms and predispose to infection of the entire urinary tract. Local palliative measures and bladder decompression become urgent procedures for immediate relief. Although the lesions grouped

under the heading of esthiomene represent swellings due to edema, a good deal of the deforming swollen lesions are made up of fibrous tissue. Healing of local ulcerations may reduce the edema present

TABLE 8.—LYMPHOGRANULOMA VENEREUM: CLINICAL DATA OF 33 MALES WITH GENITAL LESIONS.

Classification.	No. of cases.	Average age.	Average duration of lesion.	Type of treatment.	Average duration of treat.	Aver. No. of inj.	Results.			Pos. Wass.	Pos. G. C.	Pos. Ducrey.
							Excellent.	Good.	Poor.			
A. Erosion corona glans penis (small)	12	38	14 wks.	Frei antigen 6 Tartar emetic 1 None 6	11 wks.	8	6	.. .. ..	 6	9	3	4
B. Ulceration glans, lymphchancre	10	34	9 mos.	Frei antigen 5 Tartar emetic 2 Operative 2 None 1	26 wks.	24	1	1 1	3 1 2 1	7	4	1
C. Paraphimosis lymphedema	2	28	2½ mos.	Frei antigen 2	22 dys.	8	..	1	1	1	2	
D. Herpes glans	2	30	2 wks.	Frei antigen 2	4 wks.	7	2					
E. Chronic ulcer shaft	1	31	1 mo.	None								
F. Multiple ulcerations glans	1	31	1 mo.	None								
G. Bubonulus shaft	1	26	3 wks.	Frei antigen 1	2 mos.	21	1					
H. Urethral fistula perineum	1	54	20 yrs.	Frei antigen 1	4 mos.	32	..	..	1			
I. Urethritis	3	24	4 wks.	Frei antigen 3	4 wks.	6	3					

but will invariably leave the thickening due to fibrosis entirely unaffected. Thus, one must be content with the healing of open ulcerations and eventually resort to surgical removal of obstructing or deforming lesions. Operative procedures are contraindicated in the presence or even suspicion of the presence of an inflammatory focus.

Discussion. An analysis of all forms of treatment used in this group of 300 cases reveals the following (Table 9):

Approximately 33% of the cases seen, heal spontaneously without any treatment. These cases were observed among the glandular group, which represents the mildest form of this disease. No spontaneous cures were seen among the two other groups.

When any method of local treatment is used about 46% of the cases have good results when the treatment is carried out over a period of at least 7 or 8 months. In the rectal cases treated by dilatation alone, the good results may be attributed to the fact that the disease process had already spent itself when the treatment was begun.

The best results were obtained by the use of Frei antigen intra-

venously in the manner described (82%). The best results were obtained in the glandular group, although the symptomatic and systemic relief in the rectal and genital cases deserves mention. Although no complete cure was obtained in the rectal group by the use of Frei antigen alone, the disease did not progress after this form of treatment was instituted.

TABLE 9.—LYMPHOGRANULOMA VENEREUM. RESULTS OF TREATMENT.

		Glandular.	Rectal.	Genital.	Total.
Frei antigen	Healed	119	0	16	135 (67%)
	Good	17	7	8	32 (15%)
	Poor	7	18	15	40 (18%)
	Total	143	25	39	207 (100%)
Other methods of treatment	Healed	2	0	1	3 (5%)
	Good	12	10	1	23 (41%)
	Poor	10	15	5	30 (54%)
	Total	24	25	7	56 (100%)
No treatment	Healed	4	0	0	4 (11%)
	Good	8	0	0	8 (22%)
	Poor	7	5	13	25 (67%)
	Total	19	5	13	37 (100%)
Total		186	55	59	300

Summary and Conclusions. 1. The results of treatment of 300 cases of lymphogranuloma venereum are reported.

2. Two hundred and seven cases were treated by means of Frei antigen intravenously. Local palliative and radical surgical measures were used in the remaining 93 cases.

3. A uniform routine for the intravenous administration of Frei antigen is suggested. The patients receive 0.3 cc. of infiltered antigen, the same as that used for skin testing, on alternate days.

4. Various types of reactions to the initial intravenous injection are described. No alarming untoward reactions were observed in any case.

5. The rationale for the therapy of lymphogranuloma is based upon the fact that this disease is systematic in nature, even though its localized manifestations are mainly lesions in the pelvic region.

6. All of the localized manifestations of the disease are the results of inflammation in any of its stages and range from acute exudative processes to the final chronic proliferative or fibrotic conditions of the various structures affected.

7. Surgical treatment alone or palliative treatment alone have proved inadequate for the complete cure of this disease.

8. Surgical intervention is indicated only after all local evidence of any inflammation has subsided.

9. In general, the most useful local procedures in all the lesions

seen in lymphogranuloma are conservative ones, in combination with Frei antigen intravenously.

10. For the inguinal adenopathies, aspiration of inguinal abscesses where necessary and intravenous Frei antigen have been found sufficient for treatment.

11. For the rectal lesions, temporary or permanent colostomy as indicated and dilatation where possible, in combination with local palliative and systemic Frei antigen intravenously, are advised.

12. Intravenous Frei antigen was found to be the most useful single method of therapy.

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A CASE OF FATAL SUBACUTE MYOCARDITIS OF UNKNOWN ETIOLOGY.

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The case presented in this paper is that of a middle-aged woman who died suddenly following the subtotal excision of a simple colloid goiter. It is of interest because the only significant finding at autopsy was a most unusual type of myocarditis. It is thought to be worthy of report because it is impossible to assign the responsibility for the myocardial damage to any of the known causes of myocarditis.

Case History. The patient, a woman of 50, had worked in a tuberculosis sanatorium for approximately 30 years, at first as a nurse and later as a laboratory technician. She was under constant medical supervision for this period. The history which follows was obtained through the kindness of Dr. C. D. Parfitt, Loomis Sanatorium, Loomis N. Y.

As far as is known, the patient was never known to have had rheumatic fever or any other serious illness until 1907, when at 20 years she experienced several small hemoptyses. She entered a sanatorium, where tubercle bacilli were found in her sputum. With adequate treatment her condition improved and eventually she was able to take training as a nurse. She nursed in one sanatorium uninterruptedly until 1916 when she obtained a position as laboratory technician at another sanatorium.

In 1925, a hysterectomy for myomata was followed by a pelvic abscess which drained for 3 weeks. Her recovery was otherwise uninterrupted, she gained weight, resumed work and lived a regular, fairly active life until 4 months later, when she suffered another small hemoptysis, unaccompanied, however, by cough or sputum. After 9 weeks in bed she returned to work. Five years later, in 1930, she again coughed up a small amount of blood, but examination of the chest revealed only a very slight residual lesion at the apex of the right lung and a somewhat more diffuse involvement on the left side above the third rib.

During the year before her death the patient was, to all appearances, in excellent health and her exercise tolerance was good. From time to time she complained of a sensation of fullness in the throat. She had had a small goiter for years, but there were no symptoms of hyperthyroidism. In September, 1937, as the goiter appeared to be increasing in size, a subtotal thyroidectomy was performed. Physical examination before operation revealed a normal cardiovascular system. Electrocardiograms were not taken. The temperature was normal and the pulse rate not elevated. The patient's postoperative condition was satisfactory and she was given only a moderate amount of sedative drugs. Eighteen hours after operation her breathing became irregular, she gasped a few times and died suddenly.

Autopsy. Autopsy (A–321–37) included examination of the thoracic and abdominal organs, the brain and the spinal cord. The neck organs were not removed except for remnants of thyroid tissue, but were examined thoroughly *in situ*. The findings of interest were as follows:

The body was that of a well-nourished but not obese woman. At the base of the neck anteriorly was a recent collar incision. The tissues in this region were infiltrated with dark, jelly-like blood clot, and a small amount of blood had tracked down through the superior mediastinum into the layers of the pericardial sac, and laterally on either side under the layers of the pulmonary ligaments to the mediastinal surfaces of both lungs. There was a small nodule of thyroid tissue on the right side, weighing 12 gm. and a similar nodule on the left side weighing 6 gm. Fibrous adhesions were present at the apex of the left lung and a small, firm nodule was felt in this region which on section proved to be a grayish, fibrous scar from which fibrous strands radiated into the surrounding lung tissue. Fibrous adhesions covered the antero-lateral surfaces of the right lung and at the base was a pale purplish area of superficial collapse.

The heart weighed 295 gm. It was normal on external examination. The endocardial surfaces were smooth and glistening. The valve leaflets were thin and pliable, except along the free borders of the mitral valve where there was some slight whitish, fibrous, nodular thickening. The coronary arteries were freely patent and showed only very slight sclerosis. The cut surface of the myocardium was pale brownish with a few barely distinguishable small, white, fibrous flecks in the left ventricular wall near the base.

The sigmoid colon was the site of many diverticula. The uterus had been removed at a long-previous operation. All the other organs were essentially normal. No obvious cause of sudden death could be found.

Microscopic Examination. Several sections from the anterior wall of the left ventricle and the interventricular septum were stained with hematoxylin-eosin and various special stains. They showed numerous focal lesions of various sizes, some of which were perivascular but mostly not related to blood-vessels (Fig. 1). The myocardial fibers in such places had disappeared leaving elongated patches of irregular outline infiltrated with lymphocytes. Macrophages and plasma cells were present in smaller numbers and there were occasional neutrophils. Around the boundaries

of these areas were fragments of necrotic muscle; some were multinucleated, with their pyknotic nuclei scattered throughout the cytoplasm in a haphazard fashion, while other fragments were pale and completely anuclear. There were also in each focus several large, oval cells whose many nuclei were distributed around the periphery at one pole, giving them a striking resemblance to typical Langhans giant cells (Fig. 2). These were histologically similar to, if not identical with, true foreign body giant cells. The plump oval nuclei of young proliferating fibroblasts were also present. All these elements were disposed on a pinkish, thready, fibrillar, connective tissue background, composed in part of the remnants of the sarcolemma sheaths of the necrotic muscle and in part of newly formed connective tissue.

The muscle fibers between the focal lesions showed some loss of their cross-striations and some nuclear swelling. In several situations the fibers were spread apart as if by edema fluid, and here and there loosely arranged lines of lymphocytes and macrophages lay between them. The coronary vessels within the myocardium showed no significant inflammatory or degenerative change. In a few there were small, spurlike projections of the intimal coat which were made up of pale eosinophilic, subendothelial, granular material. Sections (Levaditi and Ziehl-Neelsen methods) showed no spirochetes or acid-fast bacilli. A search for other microörganisms was carried out on sections stained by the Gram method but no bacteria were found.

Microscopic examination of the thyroid tissue removed at operation, as well as that which remained at autopsy, showed encapsulated nodules composed of acini containing much colloid and lined by flattened, epithelial cells. Some nodules had undergone cystic degeneration in their central portions. In none of the sections was there any evidence of hyperplasia.

Examination of microscopic sections of the liver revealed small, pale areas of recent focal necrosis without evidences of inflammatory reaction. Sections of the brain revealed a small amount of patchy gliosis surrounding an area of old focal necrosis measuring approximately 1 mm. in diameter in the head of the right caudate nucleus. Sections of other organs showed nothing of significance with relation to the myocarditis.

Discussion. It is reasonable to suppose that this patient died as a result of the widespread myocardial lesions which have been described; clinical evidence of postoperative shock or laryngeal obstruction was lacking and a complete postmortem examination failed to reveal any of the usual causes of sudden death. The minute area of necrosis in the caudate nucleus was of very long standing, as evidenced by the surrounding gliosis and could not be related to the patient's sudden death. The focal necrosis of the liver was of recent origin. What relation, if any, either of these lesions bears to the myocarditis is not clear. It is evident that the myocarditis was of an unusual type. The patient was under competent medical supervision for 30 years previous to her death and during that period no sign of cardiac disease was manifested, and there was no indication of any condition which might have been etiologically related to the myocarditis. There was nothing in the history nor in the autopsy findings to suggest that an acute, infectious disease was the cause of the myocardial damage. The absence of pericardial and endocardial involvement as well as the histologic

FIG. 1.

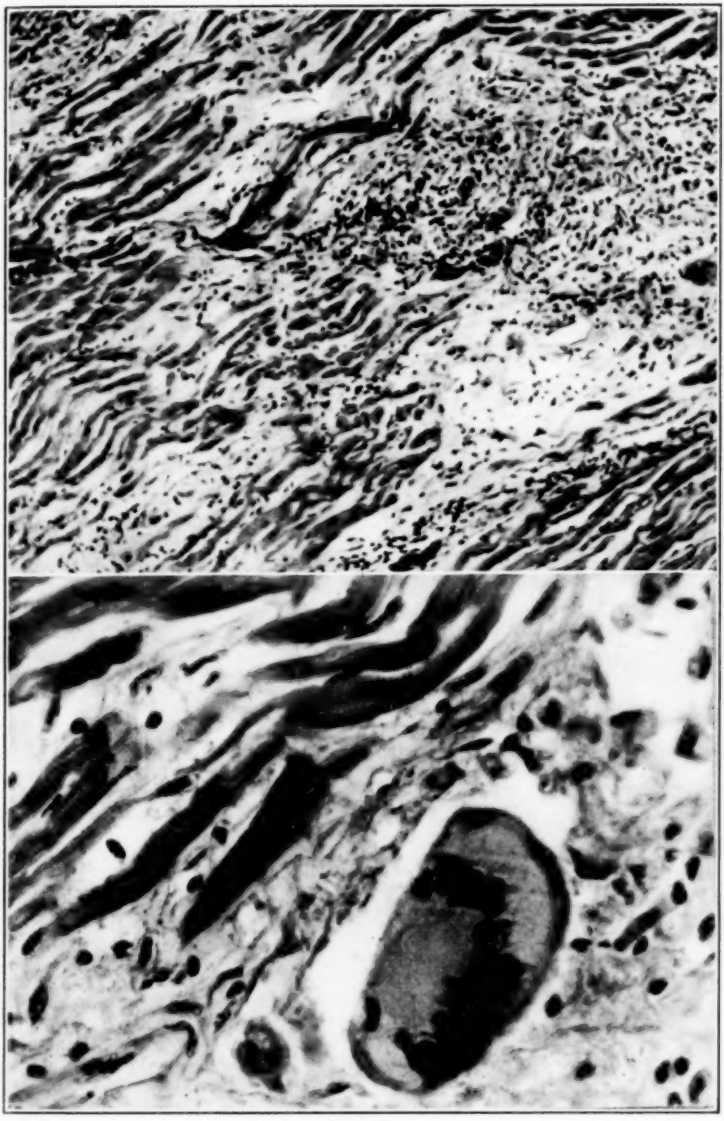

FIG. 2.

FIG. 1.—Section of the heart. An elongated patch is seen in which myocardial fibers have disappeared and are replaced by lymphocytes, macrophages, plasma cells and proliferating fibroblasts. There are also fragments of necrotic muscle, some of which are multinucleated. Hematoxylin-eosin, × 100.

FIG. 2.—Section of the heart under high magnification. There is a large oval giant cell with peripherally distributed nuclei, resembling a typical Langhans giant cell. Hematoxylin-eosin, × 400.

appearance of the myocardial lesions precluded a diagnosis of rheumatic myocarditis. The state of the coronary vessels and the widespread focal distribution of the lesions showed that the condition was not ischemic in nature. It is necessary, therefore, to consider the rarer causes of inflammatory changes in the myocardium.

In 1916, Fahr[3] described the finding of fragmentation and dissolution of the cardiac muscle fibers with round-cell infiltration and fibrosis in persons with goiter. Since that time the association of myocarditis and goiter has been reported in only a small number of cases.[7,9,12,18] In all such cases, however, the myocardial change was found to be associated with severe hyperthyroidism, but in the present case the patient's goiter was both symptomatically and histologically non-toxic. It seems reasonable, therefore, to conclude that the cardiac lesions were not due to it.

Hutchinson-Boeck's disease,[10,13] which is known by a variety of names, including sarcoidosis, lupus pernio and benign lymphogranulomatosis, is a condition characterized by the development of chronic granulomatous lesions usually confined to the skin and lymph nodes but often widely disseminated through the body and even involving the heart. It is believed by many to be a tuberculous manifestation; the lesions are rare in the heart and in none of the cases reported was the heart alone involved. The cardiac lesions in the present case lacked the epithelioid-cell proliferation characteristic of Hutchinson-Boeck's disease and presented a marked inflammatory reaction as well as evidences of necrosis, neither of which is found in this condition. For these reasons a diagnosis of Hutchinson-Boeck's disease could not be supported.

Syphilitic myocarditis, according to Warthin,[17a,b] is characterized by degenerative changes in the muscle fibers with a subacute infiltration of lymphocytes and plasma cells between the fibers. In some acute cases, monocytes and neutrophils are seen. In a case reported by Hamman and Rich[8] there was actual necrosis of the muscle fibers. The occurrence of a syphilitic arteritis of the larger coronary vessels and an "endoperiarteritis" of the smaller branches is stressed by Warthin, Vaquez[16] and others. In the present case, no such vascular lesions were found. Serologic tests for syphilis were not done but as the lesions were focal in distribution, as no spirochetes were found in sections stained by the Levaditi method, as there was an absence of syphilitic lesions elsewhere in the body and as there was no history of syphilis, one must conclude that a syphilitic origin for the condition is most unlikely.

At the time of her death this patient had a healed tuberculous lesion at the apex of the left lung and her history showed that she had suffered from hemoptysis several times in the past, the most recent occasion being 8 years before death. The possibility of a

tuberculous origin of the myocarditis must therefore be considered, though tuberculous myocarditis is extremely rare in man. If a tuberculous infection is to reach the myocardium it is apparent that it must do so either by extension through the pericardium, or by hematogeneous spread from a distant focus. The autopsy findings are against both possibilities in this case. No mediastinal tuberculosis was present, and the only possible extracardiac focus of infection, that at the apex of the left lung, appeared to be definitely healed. Furthermore, if hematogeneous dissemination of tubercle bacilli had occurred, one would expect to find tuberculous lesions in other organs but in this case no such lesions were found. The histologic appearance of the lesions, also, did not support a diagnosis of tuberculous disease: there was no evidence of caseation and no epithelioid-cell proliferation; some of the giant cells were very similar to those of tuberculosis, but can be regarded equally well as having been formed in response to the stimulus of an irritant of non-tuberculous nature.

Under the name of subacute interstitial myocarditis several French investigators have described a condition which they believe to be an atypical form of tuberculous disease. The case of Gallavardin and Gravier[5] was that of a man of 33 who died of rapidly progressive heart failure. Autopsy revealed tuberculous peritonitis and a healed tuberculous process at the apex of one lung. Microscopic examination of the heart showed small islands where the muscle fibers were fragmented and decolorized with elsewhere large areas of interstitial involvement in the form of dense fibrosis with a few inflammatory cells. The authors reported the case as one of subacute interstitial myocarditis probably of tuberculous origin, but emphasized the non-specific histologic character of the lesion.

This case of Gallavardin and Gravier has many points of similarity to others of still more obscure nature. In 1899, Fiedler[4] reported 4 cases under the title of subacute interstitial myocarditis. The clinical picture was one of rapidly progressive heart failure and autopsy showed a diffuse interstitial cellular infiltration of the myocardium. Since that time somewhat similar conditions have been described under such titles as "isolated myocarditis," "idiopathic myocarditis," "primary myocarditis," and "Fiedler's myocarditis." In the majority of such cases the heart was hypertrophied, the chambers dilated and the organ flabby. There was no pericardial change and the valves were normal. Mural thrombi secondary to the myocardial lesions were not rare. The cut surface of the heart muscle in some cases showed grayish streaks and flecks while in others it appeared normal. Microscopic examination showed a diffuse infiltration of the interstitial tissue by lymphocytes, plasma cells and macrophages. Some authors reported a predominance of eosinophils. Young fibroblasts and areas of

fibrosis were seen. In some cases there were minimal degenerative changes in the muscle while in others there was necrosis of fibers. Bailey and Andersen,[2] in a review of the literature on this subject, noted the description of multinucleated fragments of muscle cells. de La Chapelle and Graef[11] mention the description in Saltykow's case of "cells thought to be degenerating forms of muscle cells .... which are also found forming giant cells." The majority of investigators, however, regarded the primary change as interstitial.

In these cases there was no evidence that the myocardial damage was due to any of the usual causes. A history of rheumatic fever or other infectious disease could not be obtained, and the coronary arteries showed no significant arteriosclerotic narrowing. An infectious or toxic etiology was suggested by Aschoff,[1] and von Gierke[6] believed the lesion in his case to be a syphilitic manifestation. Bailey and Andersen[2] have been impressed with the frequency of the report of an antecedent or coëxisting infection such as a carbuncle, an infected burn or acute gonorrheal urethritis. Other authors regarded the cases they reported as having a specific but undetermined etiology.

Scott and Saphir,[15] in 1929, collected 30 of these obscure cases from the literature and added 2 of their own. It would appear that they regarded such cases as representing a pathologic entity. In the writer's opinion, this concept is not warranted. The only factors common to all are rapidly progressive myocardial failure or sudden death and an acute or subacute inflammation of the myocardium in the absence of any known cause of myocardial damage. The attribute of obscurity cannot be considered as a justification for grouping these conditions together as manifestations of a single disease. It appears probable that the group is a heterogeneous one, including atypical varieties of tuberculous, syphilitic and rheumatic myocarditis as well as certain other inflammatory conditions of unknown and probably variable causation. This case, therefore, is presented as one of subacute inflammation of the myocardium of unknown etiology. It is of interest to note in this connection that Rich,[14] who examined sections of the heart from the case under discussion, stated that he had seen 6 others precisely similar, in which there was no constant association with active tuberculosis, syphilis or rheumatic fever.*

Summary. A case is presented in which sudden death after subtotal excision of a simple colloid goiter was found to have been associated with myocarditis of an unusual type. Microscopic examination of the myocardium revealed many small foci of subacute inflammation in which muscle fibers had disappeared. Giant

* Since this paper was submitted for publication, Jonas (Bull. Johns Hopkins Hosp., **64**, 45, 1939) has reported 5 cases of "granulomatous myocarditis." These were presumably included in those referred to by Rich.

cells were prominent among the mononuclear inflammatory cells and proliferating fibroblasts in these areas.

The origin of the cardiac lesions is discussed and it is concluded that they were not related to the patient's goiter and did not seem to be due to tuberculosis, syphilis, rheumatic fever or Hutchinson-Boeck's disease. The case is presented as one of subacute myocarditis of obscure etiology.

My thanks are due to Dr. G. Lyman Duff for his assistance in the preparation of this paper.

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PROGNOSIS IN DIABETIC COMA: BASIC IMPORTANCE OF MENTAL STATE.

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Any one who has much to do with diabetic coma soon comes to realize that even the best therapy remains highly unsatisfactory in the majority of unconscious cases. Practically no therapeutic progress has been made in this field since the early days of insulin, nor are we any nearer the answer as to why the unconsciousness of diabetic ketosis regularly carries such a high fatality rate. From the findings presented in subsequent paragraphs it would seem that by far the most important factors in coma prognosis, even with the best of treatment, are the depth of the stupor and its duration before treatment is instituted. The duration of acidosis (without complete

unconsciousness) seems to be of minor importance, but, once central nervous system damage has produced the unconscious state, chances for reversal of this damage seem to diminish rapidly. Nor does elimination or improvement of the ketosis offer any great assurance of recovery. The amounts of insulin, glucose, and alkalies administered seem within reasonable limits to affect the prognosis much less than do the depth and preceding duration of the stupor.

In order to gain a clearer picture of the prognosis and factors behind the high coma mortality, a careful analysis was made of the clinical records of all diabetic ketosis and coma cases admitted to the Cincinnati General Hospital for the 15 years from 1923 to 1937. Facts taken from the records included age, sex, color, duration of acidosis before admission, mental state on admission, blood and urine sugar determination, blood alkali reserve, complications on admission and after admission, treatment with insulin, glucose and alkalies, and outcome and autopsy. Various groupings of the cases were made in order to test for significant relationships and the relative importance of the different factors. From all the 15 years' records only 92 cases were found which satisfied clinical and laboratory requirements for impending or actual coma. Those with mild acidosis, without significant mental symptoms, were not included since adequate and satisfactory methods of treatment are already available and in general use.

The duration of the ketosis was reckoned from that point at which persistent vomiting and drowsiness began. As the ketosis progressed, certain mental states developed by which the patients were classified as: 1, *conscious*, those who were drowsy but could answer questions and take fluids by mouth; 2, *semi-conscious*, those who responded to peripheral stimulation but were unable to answer questions or take fluids by mouth, and, 3, the *completely unconscious*, those who did not respond to any stimulation.

Of the total 92 cases studied, 51 were white and 41 colored. The white patients, 28 of whom died, presented a mortality of 54.9%, while 19 (46.3%) of the colored died. In the out-patient dispensary and diabetic clinic for ambulatory cases, white patients outnumber the colored 2 to 1, while with the diabetic coma admissions the proportion is only 5 to 4. Whether this represents a greater severity of the disease among the colored or only greater neglect in handling cannot be said. It is of interest, however, to note the greater severity of the disease in northern colored reported by Mills,[6] who found the diabetic death rate actually higher among colored than white in the north. Joslin[5] also found the disease increasing more rapidly in the colored than in white.

There were 28 males and 64 females. Of the males, 20 were white and 8 colored. Of the females, 31 were white and 33 colored. Eight of the 28 males died (28.5%). In the female group of 64

there were 39 deaths (60.9%). The preponderance of female cases and deaths is unusually striking. Several years ago it was thought that males were more predisposed to diabetes than females, but in recent years the reverse has been shown to be true.[5] Attending the out-patient diabetic clinic in 1937, the ratio of males to females was 1 to 1.7, while in the coma group the ratio was 1 to 2.3. In the out-patient clinic group the ratio of white males to females was 1:1.37, while with the colored it was 1:2.72.

In an analysis of the cases according to age groups, another very striking sex factor is found. Ketosis and coma in females seem particularly prone to occur during puberty and at the menopause, and at those times to be more highly fatal. Table 1 brings out this fact rather clearly. In the 40–49 year age group there were 16 females of whom 13 died (81.2%). Of the 5 male patients in this age group all recovered. Puberty in the male brings a heightened incidence of coma, but in boys of the 10–19 year age group 8 out of 9 cases recovered, while with the girls 6 out of 11 died. These findings fit in well with the known fact that disturbances in other endocrine glands bring greater severity and frequency of diabetes.

TABLE 1.—COMA AND PRE-COMA CASES CLASSIFIED BY SEX, AGE, AND OUTCOME.

Age group (years).	Males.		Females.		
	Recovered.	Died.	Recovered.	Died.	Mortality. %
0– 9	2	1	0	0	
10–19	8	1	5	6	55
20–29	1	0	8	4	33
30–39	1	1	5	5	50
40–49	5	0	3	13	81.2
50–59	2	3	3	5	62.5
60+	0	2	3	6	67

TABLE 2.—MENTAL STATE, AGE, MORTALITY, AND DURATION OF KETOSIS SYMPTOMS PRECEDING HOSPITAL ADMISSION.

Age group. (years).	Duration (in hours) of mental symptoms preceding hospitalization.			
	Conscious and semi-conscious group.		Unconscious group.	
	Recovered.	Died.	Recovered.	Died.
0– 9	?–12	10		
10–19	1–2–10–20–14–18–10–18	5	20–12	24–36–6–15–?–18
20–29	10–18–12–12–36–12–24–36		12–16	15–?–10–8–15
30–39	?–12–?–8	20–24	15–10	15–18–24–9
40–49	?–10–?–8–24	24–?–12–12	12–16–12–6	?–16–18–16–12–48–36
50–59	12–8–8–24	?	12–8	17–?–36–14–12–18
60+	18	18	10	8–12–?–?–?–?–?–15
	Aver. = 14.9 hrs.	Aver. = 15.6 hrs.	Aver. = 11.9 hrs.	Aver. = 18.5 hrs.
	Average mortality Under 40 years = 14.4% 40 years and over = 35.3%		Average mortality Under 40 years = 71.4% 40 years and over = 75%	

(?)—Duration of ketosis unknown. Other numbers represent hours in ketosis preceding hospital admission.

In Table 2 is presented evidence of the great importance which attaches to the degree of central nervous system damage brought on by ketosis. Duration of the ketosis is shown for the individual

cases, with grouping according to mental state on admission and whether death or recovery ensued. Of the 92 cases, 49 were completely unconscious on admission, with an average of 16.2 hours in ketosis before admission and a mortality of 73.5%. The average duration of ketosis in the semi-conscious group of 33 was 15 hours, and the mortality 33.3%. The conscious group of 10 had been in ketosis for an average of 13 hours and included no deaths. From these findings it is evident that progressive and often irreversible changes in the central nervous system play a very important part in the prognosis of diabetic coma, for the mortality sharply increases as the patient progresses from the conscious to the unconscious state and as the ketosis continues for additional hours.

Table 3, showing further grouping of the material of Table 2, indicates still more strikingly the importance of the extent and duration of brain damage. So long as the patients are not completely unconscious on institution of proper therapy, the mortality remains low regardless of the preceding duration of the ketosis. But if complete coma has developed, even for only a few hours, prognosis

TABLE 3.—MORTALITY IN RELATION TO MENTAL INVOLVEMENT AND DURATION OF KETOSIS SYMPTOMS PRECEDING HOSPITAL ADMISSION.

Hours in ketosis before admission.	Mental state on admission. Conscious and semi-conscious number of cases.			Unconscious number of cases.		
	Recovered.	Died.	% Mortality.	Recovered.	Died	% Mortality
0– 8	5	1	18.2	3	4	47.3
9–14	13	3		7	5	
15–20	4	2	25.0	3	12	85.7
Over 20	0	1		0	6	

becomes much more grave. The conscious and semi-conscious patients in ketosis over 14 hours had a mortality of only 25%. But if complete unconsciousness had supervened before admission to the hospital, then a mortality rate of 47.3% was found with the 19 who had been in ketosis 14 hours or less, and an 85.7% mortality for the 21 with ketosis of longer duration. It is quite evident, then, that prognosis is largely determined by the combination of these two factors, duration of ketosis and extent of brain damage.

Let us next see what prognostic value attaches to the CO_2-combining power of the blood at the time treatment is instituted (Tables 4 and 5). For those in the conscious group, the CO_2-combining power on admission to the hospital averaged 17.1 vol. %. In those of the semi-conscious who recovered the average CO_2-combining power was 15.1 vol. %, while for those who died it was 17.7 vol. %. The unconscious group gave similar findings, with 13.2 vol. % for those who survived and 17.2 vol. % for those who succumbed. If division is made into high and low levels in an attempt to place a more exact prognostic value on the findings, no change in the results can be found. Taking only those cases with a CO_2-combining level

below 10 vol. %, we find 3 in the semi-conscious group with one death and 4 in the unconscious with only one death. And taking only those above 20 vol. % on admission, there were 4 deaths and one recovery in the semi-conscious group, and 7 deaths with one recovery in the completely unconscious. These points are strongly emphasized by the data of Tables 4 and 5 and in the summary.

TABLE 4.—BLOOD CO_2–COMBINING POWER, MENTAL STATE, AGE AND MORTALITY.

	Blood CO_2 (vol. per cent) at time of hospital admission.					
	Conscious groups.		Semi-conscious groups.		Unconscious groups.	
Years.	Recovered.	Died.	Recovered.	Died.	Recovered.	Died.
0– 9	19		20	28		
9–19	12		16,14,19,13,12,14	10,8	18,20	8,29,16,10,11
20–29	20		12,6,14,18,21		10,5.14	14
30–39	18,17		20,19	15		25,16,10,12
40–49	21,20,20		9,14,12	28,10,21	25,8,12	28,14,16,20,10
50–59	12,12		20	22	6,14	18,13,12,22
60+						28,12,19,14, 14, 32
Aver.	17.1	—	15.1	17.7	13.2	17.2

TABLE 5.—BLOOD ALKALI RESERVE LEVEL AS A PROGNOSTIC FACTOR.

	Mental state and percentage mortality.		
CO_2 (Vol. %)	Conscious % mortality.	Semi-conscious % mortality.	Unconscious % mortality.
20 or below	0	20	68.6
Above 20	0	80	87.5
Unknown	0	37.5	76.9
Total	0	33.3	73.5

Physicians and workers in the field of diabetes have been wont to attach great prognostic importance to the blood alkali reserve level in diabetic ketosis and coma. Some have even gone so far as to use this as the determining factor in defining and diagnosing coma for statistical purposes. Such an attitude seems entirely unjustified on the basis of our findings. In Table 4 are given the blood alkali reserve findings on admission for our whole group of 92 cases. Admission determinations were not made on every patient; but in those cases having such data, higher average values were found for those who later died than for those who recovered. Ketosis patients, either conscious or unconscious, may be admitted with CO_2-combining power below 10 vol. % and go on to recovery; or those above 20, or even 30 vol. % may go on to death if the brain damage has become too extensive or too prolonged. Little prognostic value would seem to reside, therefore, in the blood alkali reserve level.

Although the findings of Dillon and Dyer[3] seem to show a higher alkali reserve in the ketosis patients who recover than in those who die, a regrouping of their data on the basis of mental state shows just the reverse to be true. Among their uncomplicated ketosis

cases were 10 unconscious patients who recovered and 27 who died. The average blood CO_2-combining power on admission was 13.4 vol. % for those who recovered and 15.5 for those who died. These findings are in complete agreement with those of our series, showing the blood alkali reserve to be of no prognostic significance in coma cases who are unconscious on admission. Their mortality for this group was 73%—ours was 73.5%.

All the patients in our series received the generally accepted treatment. Insulin was always given in large and frequent doses. Large quantities of fluids, normal saline solution by infusion or intravenously, or water by mouth when possible, have been a routine part of treatment. The general treatment included stimulants, attention to the gastro-enteric tract, and external heat, according to the needs of the individual patients. A summary of treatment with reference to the amount of insulin given the first 2 hours and every 2 hours thereafter, and the amount of glucose and alkalies, according to mortality and mental state, is shown in Table 6. These findings show that the treatment given those who died was just as adequate as was that for those who recovered; 69 patients received an average of 110 gm. of glucose, with 31 deaths—a mortality of 45%. Alkalies were administered to 25 patients, of whom 15 died (60%).

TABLE 6.—TREATMENT AND COMA OUTCOME.

	Conscious.		Semi-conscious.		Unconscious.	
	Died.	Recovered.	Died.	Recovered.	Died.	Recovered.
Insulin 1st 2 hrs.	0	59 (9)	42 (12)	81 (21)	70 (35)	83 (13)
Insulin each 2 hrs. thereafter . .	0	17 (9)	28 (12)	17 (20)	31 (32)	19 (13)
Glucose . . .	0	110 (7)	96 (10)	104 (20)	105 (20)	135 (12)
Alkalies . . .	0	18 (2)	20 (3)	32 (3)	56 (12)	61 (5)

Numbers in parentheses represent number of patients.

A most detailed study of our treatment statistics fails to show any significant differences to account for recoveries or deaths of coma patients. The primary diabetic state and ketosis were adequately treated with all possible speed in every coma case. Other factors than present accepted lines of treatment must therefore determine coma mortality.

In dealing with the part complications play in coma outcome, it must be kept in mind that we are here considering only the coma itself, and not the general diabetic state of the individual. Thus, one patient was admitted in coma, with gangrene of his right foot. After complete recovery from his ketosis, his foot was amputated and he died in subsequent septicemia. This was a case of death from a complication of diabetes but in no sense a death to be considered in relation to coma statistics. In the total series of 92 cases there were 17 with complications. These included conditions affecting the coma and were mostly due to infections of various types. Of these 17 patients, 10 died. Total coma cases were about equally

divided above and below 40 years of age; but of the 10 total cases with complications, 7 deaths were among those above 40 years and only 3 below the age of 40. Included in these 10 deaths were 2 patients of the conscious group whose deaths occurred later after the ketosis had been controlled and operation for complications had been performed. These have not been classed as ketosis deaths. The only fatal cases complicated on admission by conditions usually carrying a high death rate in themselves were 3 pneumonias, 1 lobular and 2 lobar. Six of the patients who died with complications were autopsied, with findings confirming the antemortem clinical diagnoses.

Discussion. From the analysis of our 92 case histories, it is evident that the mortality in diabetic coma depends primarily on the extent and previous duration of brain damage present when treatment is begun. This central nervous system damage seems unrelated to the severity of coëxisting acidosis, but rather to pursue a course entirely unexplained by present knowledge of coma. Anoxia in the body tissues of highest metabolic activity might well explain the proneness of brain, kidney, liver and heart muscle to be most affected by the serious interference with combustion processes in diabetic coma. Further advance in coma therapy should, it seems, follow this line of investigation.

Diabetic patients with simple ketosis and little mental impairment on admission for treatment seldom die in coma. The remarkably low coma mortality figures cited in many recent articles have been obtained by dealing with early pre-coma cases of low blood alkali reserve, but with slight mental change. This class of patients differs so sharply in response to treatment from the unconscious group that it would seem wise to class them simply as ketosis or pre-coma, and reserve the term *diabetic coma* for only the unconscious cases that have such a high mortality. Present methods of treating the underlying diabetic state are highly effective in pre-coma cases, but are of little avail in a majority of instances of true coma. It would seem that an entirely new line of therapy will be needed to restore function in the tissues damaged in severe diabetic ketosis.

Many previous articles[1–4] on diabetic coma have been based largely on a classification of patients according to the CO_2-combining power of their blood. We have shown that such selection is not warranted, since this level not only fails to parallel the mental state, but has no proved relation to mortality or prognosis. In our series, the blood CO_2-combining power was higher in those who succumbed than in those who recovered just as it was in the uncomplicated, unconscious cases of Dillon and Dyer. Great advances have been made in the treatment of early acidosis and the prevention of coma since the advent of insulin. Little progress has been made, however,

in the treatment of the unconscious patient with true diabetic coma. General intensive treatment was given all of the cases reported in this series. Insulin as the mainstay of the treatment was used on all. Glucose and alkalies were given in varying amounts, and yet none of these or any other measures employed were able to reduce the mortality of the unconscious patients. It is felt that, even with the closest attention to treatment according to present knowledge, the mortality of the unconscious patient in diabetic coma will be extremely high when the duration of ketosis has been so prolonged as to produce extensive brain damage.

An interesting point which has been shown by our analysis is the frequent occurrence of diabetic coma in the female. There are more females than males with diabetes, but the number of females with coma is far greater than males. It has been noted that coma occurs more frequently during the decades which include puberty and the menopause. The male at this time does not seem greatly affected, since at puberty only one died and at the menopausal decade all recovered. The female, however, at puberty shows a slightly higher mortality (54.5%) than that of the total (51%), but at menopause this mortality rises sharply (81.2%). Such findings are most significant, and lend great weight to the idea that disturbances in other parts of the endocrine system have an important bearing on the occurrence and severity of diabetes.

Age has not been of outstanding significance in our series. In the conscious and semi-conscious group there is some increase in mortality rate above the age of 40. This increase, however, is not great, but enough to indicate that the younger diabetic has a greater chance for recovery. In the unconscious group age plays no significant part, for the mortality is high in all age groups.

Perhaps the most surprising point arising from our case study is that blood CO_2-combining capacity is of practically no prognostic value in diabetic coma. This finding is directly contrary to prevailing ideas, but seems to be adequately supported by the data presented. No further justification exists for classifying coma cases on the basis of alkali reserve level. Instead there seems every reason that they be grouped only on the basis of brain damage, and that such grouping differentiate the completely unconscious (or true coma cases) of high mortality from the pre-comatose.

Summary. 1. Duration of ketosis, with occurrence of brain damage resulting in unconsciousness, is of primary importance as a prognostic factor in diabetic coma.

2. Lack of prognostic value to be obtained from blood alkali reserve findings is evident from the data we present.

3. The usually accepted methods of treatment are inadequate in the majority of the unconscious diabetic coma patients.

4. Diabetic coma in females seems especially prone to occur at

puberty and in the menopasual decade, and to carry then an exceptionally high mortality.

5. It would seem wise to classify those patients who are unconscious as "diabetic coma," using the term "pre-coma" for all those whose mental state is a much less prominent finding.

The authors are indebted to Dr. C. A. Mills for his constructive suggestions and criticism during the course of the study and in the preparation of the manuscript.

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BOOK REVIEWS AND NOTICES.

PROCEEDINGS OF THE AMERICAN PHILOSOPHICAL SOCIETY FOR PROMOTING USEFUL KNOWLEDGE, held at Philadelphia (Vol. 80, No. 3, February 10, 1939). Contents: Measles and Scarlet Fever in Providence, R. I., 1929–1934 with Respect to Age and Size of Family. By EDWIN B. WILSON, CONSTANCE BENNETT, MARGARET ALLEN, and JANE WORCESTER, Harvard School of Public Health. Pp. 120; illustrated. Philadelphia: The American Philosophical Society, 1939. Price, 75c.

THE behavior of measles and scarlet fever in Providence, Rhode Island, during recent years is compared with previously published data of C. V. Chapin dating from 1858–1923 for measles, and A. S. Pope dealing with scarlet fever covering the period 1865–1924. Percentage distributions, attack rates, and secondary attack rates by age are discussed. An attempt was made to compute rates of incidence which even though rough, since they had to be based on estimated populations, probably give a better picture of the disease than the percentage distributions. Great attention is paid throughout to size of family. Greenwood's theory of the chain binomial was tested and found not to fit when various ways of chaining were considered. The secondary attack rate becomes direct secondary, tertiary, and quaternary if there are three possible secondary cases in a family. The two parts of the measles epidemic of 1931–1932 were compared and differences were found. Measles cases for 1916–1936 for Boston by wards were studied for periodicity and it was found that a 2-year period was not obvious either in total Boston or within the individual wards.

J. G.

TEXT-BOOK OF NEURO-ANATOMY AND THE SENSE ORGANS. By O. LARSELL, PH.D., Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 343; 232 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, $6.00.

THE increasing importance of neuro-anatomy in the medical curriculum and the necessity for simple explanations of the functions of the different parts of the nervous system are reflected in the latest addition to the texts on this subject. The general treatment is by functional systems, instead of merely anatomic units, and clinical interpretations are given at the end of nine of the chapters. A number of the figures are from the author's own studies, and there are many new diagrams, some with color. The functions of the hypothalamus and of the cerebellum are considered from the current standpoints. This is essentially a descriptive text, and directions for laboratory work are not included. There are references to current literature at the end of each chapter.

W. A.

FEMININE HYGIENE IN MARRIAGE. By A. F. NIEMOELLER, A.B., M.A., B.S., with a Foreword by WINFIELD SCOTT PUGH, B.S., M.D. Pp. 155; illustrated. New York: Harvest House, 1938. Price, $2.00.

THERE are numerous books published upon the rather vague subject of feminine hygiene, of which the author's volume is just one more. It is a small volume, with practically no illustrations. It deals chiefly with menstruation and its disorders, and venereal diseases. The background of

the book is indicated by the publisher's note that all of the illustrations are reproduced through the courtesy of Sexology Magazine. The Reviewer is further prejudiced by the fact that the author does not possess a medical degree. D. M.

CHEMIE UND PHYSIOLOGIE DES EIWEISSES. Mit Unterstützung der Stadt Frankfurt a. M. 3. Frankfurter Konferenz für medizinisch-naturwissenschaftliche Zusammenarbeit am 2. und 3. Juni, 1938. Herausgegeben von DR. R. OTTO, Geh. Med.-Rat., Direktor des Staatl. Instituts für exper. Therapie und des Forschungsinstitut für Chemotherapie, Honorarprofessor in der med. Fakultät, Frankfurt a. M., DR. K. FELIX, o. Professor für vegetative Physiologie, Frankfurt a. M., DR. F. LAIBACH, o. Professor für Botanik, Frankfurt a. M. Pp. 203. Dresden: Theodor Steinkopff, 1938. Price, Paper, Rm. 6.75.

THIS report contains the 17 reviews on the various phases of the chemistry and physiology of proteins given at the 1938 Frankfurt Conference, together with discussions and comments.

First the chemistry of the proteins (protein structure, proteins as constituents of hormones, toxins and enzymes, the influence of proteins on the transport and activity of therapeutic agents) is dealt with. The next section considers the immunologic properties of proteins. The specificity and antigenicity of proteins and their relationship to anaphylaxis and allergy are reviewed; non-specific protein therapy and the allocation of antibodies to the various protein fractions of serum are also considered. The third section discusses certain aspects of the metabolism of proteins, both in plants and in animals, and considers the rôle of proteins in nutrition. Included in this last group are such diverse topics as the detoxification of ammonia and the synthesis of alkaloids by plants, the response of plants to protein decomposition products, the technical cultivation of protein-rich yeasts, plant-breeding experiments on protein-rich "sweet" lupines and on soybeans, protein as a factor in human nutrition, and the utilization of amino acids in the animal body.

This report is markedly inferior to some other recent publications such as the reviews on proteins in the Cold Spring Harbor Symposia on Quantitative Biology. Although the papers in the third section are generally satisfactory, the first two groups, dealing with the structural and immunologic properties of proteins, are distinctly disappointing. Thus, the review on protein structure mentions neither the cyclol hypothesis nor the possible rôle of hydrogen bond formation in the establishment of cross-linkages between polypeptide chains. The discussion of proteins as constituents of enzymes is largely devoted to an exposition of the "carrier" theory of enzyme structure, relatively little being said concerning the nature of the carrier proteins themselves. The papers on immunology present only familiar old material. The most irritating feature of more than half the reviews throughout the book is their failure to give literature references. Even where bibliographies are included, the references may be solely to German work (p. 67) or may contain serious typographical errors (p. 15). More careful editing might have obviated other faults. Thus, on p. 2, the number of amino acids derived from proteins is set at 27; on p. 177, at 22. Further, one cannot detect any apparent relationship between histidine and the indolylpyruvic acid mentioned on p. 182. The statement on p. 171 that milk proteins fed to human beings have a biologic value of less than 50 is surprising. Typographical errors in addition to those on p. 15 were noted on pp. 56, 73 and 172.

Taken as a whole, the reviews are less interesting and valuable scientifically than they are for the information they give about the trends of protein

chemistry and physiology in Germany at the present time. Reviews on the more fundamental aspects of protein chemistry and physiology present nothing essentially new. Indeed, such papers frequently leave one with the impression that considerable recent significant work has not been covered. In decided contrast, the reviews which deal with the problem of increasing the domestic production of protein in the Reich are replete with references to recent work and with notations of results from unpublished studies. It is evident that Germany's attempt to become self-sufficient has influenced the nature of her scientific research. A. K.

End-results in the Treatment of Gastric Cancer. An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment. By Edward M. Livingston, B.Sc., M.D., Associate Visiting Surgeon, Bellevue Hospital, New York; Assistant Clinical Professor of Surgery, New York University College of Medicine, etc.; and George T. Pack, B.Sc., M.D., F.A.C.S., Attending Surgeon, Memorial Hospital, New York City; Assistant Professor of Clinical Surgery, The School of Medicine, Yale University, New Haven and Cornell University Medical College, New York City. With a Foreword by Bowman C. Crowell, M.D., Associate Director, American College of Surgeons. Pp. 179; illustrated. New York: Paul B. Hoeber, Inc., 1939. Price, $3.00.

The theme of this important monograph might well be stated as "nothing ventured, nothing won." The authors have clearly stated the case for gastric resection in gastric carcinoma when there is a possibility of removing the tumor-bearing area; and by their figures have emphasized the importance of an exploratory operation to determine the operability of the lesion in many cases.

The form of this monograph makes it valuable propaganda in impressing on the surgeon his own responsibility for making the decision which may add years of comfortable life to patients who are too often denied this chance. It will undoubtedly prove a stimulus also to the more uniform reporting of results.

This book should be studied by every surgeon attempting to do major surgery; and as a result it is to be hoped that surgeons will either equip themselves to take proper care of these patients or see the importance of referring them to clinics where they can be properly cared for.

I. R.

Textbook of General Surgery. By Warren H. Cole, M.D., F.A.C.S., Professor of Surgery, University of Illinois College of Medicine, etc.; and Robert Elman, M.D., Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Pp. 1031; 559 illustrations. Second edition. New York: D. Appleton-Century Company, Inc., 1939. Price, $8.00.

The second edition of this excellent textbook has brought up to date many of the methods of treatment of surgical patients. It has, like the first edition, full bibliographies and has the virtue of leading the inquiring student to read the original articles from which information has been drawn. Unfortunately there has been no important change made in the section on appendicitis and a right rectus incision is still advised, but since this is a text for students, the young surgeon may, by the time he is ready to operate, have received sufficient training to lead him to use the safer McBurney incision. Of the many textbooks written for the students of surgery, this one can be placed very high on the list. I. R.

CLINICAL PATHOLOGICAL GYNECOLOGY. By J. THORNWELL WITHERSPOON, B.S. (Princeton), B.A. and M.A. (Oxon.), M.D. (Johns Hopkins), Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Pp. 400; 271 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $6.50.

THIS book, based upon the author's teaching course, deals with the common pathologic conditions of the various parts of the female generative tract, discusses the anterior pituitary gonadotropic and ovarian hormones, and the gynecologic disorders of early pregnancy. Each subject is presented so that both the pathologic and clinical pictures of the same disease are discussed at the same time.

The author offers it as an introduction to pathologic gynecology rather than as a textbook. The material is well arranged; the illustrations are adequate in number and are well selected, line drawings are supplied in appropriate places. The index is unusually complete for a volume of its size. The book is well rounded in its treatment of the various subjects, though by no means profound. It would seem to be a book ideally suited for the undergraduate medical student, and equally valuable for those graduates who plan to take the examination given by the American Board of Obstetrics and Gynecology. D. M.

PROBLEMS IN PRISON PSYCHIATRY. By J. G. WILSON, M.D., Senior Surgeon (Retired), United States Public Health Service; Director, Division of Hospitals and Mental Hygiene, Department of Welfare of the State of Kentucky, and M. J. PESCOR, M.D., Clinical Director, United States Public Health Service Hospital, Fort Worth, Texas. Pp. 275; 7 tables. Caldwell, Idaho: The Caxton Printers, Ltd., 1939. Price, $3.00.

WITH insight born of large experience, the authors have written concisely and lucidly the first book wherein prisoners are classified on a psychologic basis. Its contents are considered under the following chapter headings: Historical Consideration; A Difficult Problem; Attempt to Solve the Problem; The Normal Prisoner; The Feeble-Minded Prisoner; The Psychoneurotic Prisoner; The Psychotic (Insane) Prisoner; The Neuropathic Prisoner; The Homosexual Prisoner; The Recidivist; Discipline in Prison; The Value of Imprisonment; Appendix: Landmarks and Dates in the Development of Prisons.

The real mental defective is accepted as incapable of reformation, unsuited for prison discipline, and should be transferred to a special institution, wherefrom he should not be made a parolee, unless under continuous, competent supervision. In the psychoneurotic group, there is often the background of disrupted homelife and poor health; frequently, such persons feign illness to gain sympathy and for failure to meet environmental difficulties, but such trickery is done unconsciously and so is not true malingering. Among the psychopaths, may be found borderline psychotics, perverts, hoboes, alcohol and drug addicts, cranks and malingerers. The psychotic prisoner comes in for discussion both as to legal insanity and medical insanity; imprisonment as a cause of insanity; insanity as a cause of crime; prison psychoses; malingered insanity; suicide in prison; treatment. Homosexuality is the darkest spot in prison life, with its indulgers, according to different observers, numbering from 10 to 30% of the inmates; extreme measures must be employed to lessen the vice; Russia and Mexico are attacking the problem by "colonization in which the families of the convicts are included or by regular private visits of the husband and wife at stated intervals." "There is no clearly defined, uniform prison policy in the United States . . . . Progress in administration along modern lines is impeded by backward and archaic legislature." The value is stressed of spending the last year of a long sentence in a prison camp; of shorter sen-

tences and more efficient parole officers; of more probation, with its numerous advantages safeguarded by additional trained probation officers.

On the wrapper it is stated this volume will appeal to judges, probation and parole officers, social welfare workers, psychiatrists, wardens and staff officers, professors and students of sociology and abnormal psychology. With this the Reviewer is in full accord and begs to add, its compulsory perusal by all trustees on prison boards. N. Y.

PHYSIOLOGY OF THE UTERUS. With Clinical Correlations. By SAMUEL R. M. REYNOLDS, M.A., PH.D., Fellow, John Simon Guggenheim Memorial Foundation, The University of Rochester School of Medicine and Dentistry, Rochester, etc. With Forewords by GEORGE W. CORNER, M.D., Professor of Anatomy, University of Rochester School of Medicine and Dentistry, and ROBERT T. FRANK, M.D., F.A.C.S., Consulting Gynecologist, Mt. Sinai Hospital, New York, etc. Pp. 447; 44 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, $7.50.

THIS book presents a connected account of many facts of uterine physiology which have not hitherto been assembled. As such it will be welcomed by students of reproductive physiology and interested clinicians. It ought also to be read by those who are unaware of the vitality of this branch of general physiology; that the last decade can account for most of the 1200 references to investigative work considered by Doctor Reynolds is surely proof of the attraction—and importance—of the questions for which so many workers have been seeking answers. The author's own researches, moreover, and his scholarly and very readable review of current concepts of uterine physiology demonstrate anew what an alert mind can do for a subject which, at first glance, is apt to be regarded generally as one of very limited interest.

The phenomena of uterine motility and growth are arranged in relation to the menstrual and the reproductive cycles. Under each of these divisions data which have been drawn from physiologic, pharmacologic, biochemical and endocrine techniques of study are systematically considered. Such a presentation might readily be merely a tedious compendium of facts. Instead, by a critical but fair and attractive selection of data and ideas, the author has woven a patterned account of his subject which should be provocative of much new interest in this field. In particular, it should stimulate obstetricians and gynecologists to restudy certain clinical problems, the physiologic bases of which are clearly and logically defined here for the first time.

The format of the book is attractive, and the typography remarkably free of blemishes. C. B.

MENTAL DISORDERS IN URBAN AREAS. An Ecological Study of Schizophrenia and Other Psychoses. By ROBERT E. L. FARIS and H. WARREN DUNHAM. Pp. 270; 2 charts, 96 tables and 37 maps. Chicago: The University of Chicago Press, 1939. Price, $2.50.

THIS is a further contribution in the excellent University of Chicago sociologic series. The foreword by H. Douglas Singer expresses the purpose of this study and publication—"that the environmental setting is an important factor in the etiology of these illnesses (psychoses) has long been recognized; the facts here recorded emphasize the importance and establish for it a statistical validity." Fundamentally the whole study is a good conservative pioneer study in the social aspects of mental disorder. The Chicago area is studied in detail and contrasted with a similar study of Providence, R. I. The authors emphasize the disorganization of the industrial city as contributing to interference with normal family, community

and social life resulting in a causative situation predisposing to and possibly causing schizophrenia and other mental disorders. They do not find this true in reference to organic psychoses.

Psychiatrists will find points with which they will disagree as to the explanations the authors present as reasons why certain psychotic syndromes occur more frequently in certain city areas. But all serious students—psychiatric or otherwise—will find this book an excellent volume to inform them as to the actual picture presented by city life and its influences on psychiatric cases and sociologic conditions. Everyone who is interested in etiology, frequency, distribution, mental hygiene, public health, and any social aspects of psychiatry in a large community should be familiar with this work. L. S.

PERSONAL AND COMMUNITY HEALTH. By C. E. TURNER, A.M., Sc.D., Dr.P.H., Professor of Biology and Public Health in the Massachusetts Institute of Technology, etc. Pp. 652; 127 illustrations, 17 tables, and 4 colored plates. Fifth Edition. St. Louis: The C. V. Mosby Company, 1939. Price, $3.00.

THIS book is designed to serve as a textbook of health instruction at the university level. The broad and ever-widening field of knowledge pertaining to health makes the selection of material a difficult task, which the author has well performed. Some of the more important work of the past few years is included in this new edition, which is thoroughly accurate and clearly written, and the book should serve its purpose very well. The first part of the book is devoted to personal health and hygiene and the second part to community health; together they cover the various aspects of health which should be included in a well-rounded university education. The success of the book is indicated by the fact that a new edition has been published every four or five years since 1926. G. R.

NEW BOOKS.

A Textbook of Obstetrics. With Special Reference to Nursing Care. By CHARLES B. REED, M.D., F.A.C.S., Associate Professor of Obstetrics, Northwestern University Medical School; Head of Obstetrical Department, Wesley Memorial Hospital, Chicago, and BESS I. COOLEY, R.N., Supervisor and Instructor, Department of Obstetrics, Wesley Memorial Hospital, Chicago. Pp. 476; 209 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $3.00.

Practice of Allergy. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 1082; 338 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $11.50.

Studies from the Center for Research in Child Health and Development, School of Public Health, Harvard University. I. The Center, the Group under Observation, Sources of Information, and Studies in Progress. By HAROLD C. STUART, M.D., and Staff. (Monographs of the Society for Research in Child Development, Vol. IV, No. 1, Serial No. 20). Pp. 261; 66 illustrations. Washington, D. C.: Society for Research in Child Development, National Research Council, 1939. Price, $1.75.

Rétine Humaine et Phénomènes Entoptiques. By DR. E. P. FORTIN. Pp. 207; 127 illustrations (3 in color). Buenos Aires: "El Ateneo," n.d.

The Endocrine Glands. By MAX A. GOLDZIEHER, M.D., Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital, New York, etc. Pp. 916; 271 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, $10.00.

Investigations sur le Glaucome (Essais). By DR. E. P. FORTIN. Pp. 47; 33 illustrations (7 in color). Buenos Aires: "El Ateneo," n.d.

Varicose Veins. By ALTON OCHSNER, B.A., M.D., D.Sc. (HON.), F.A.C.S., William Henderson Professor of Surgery and Director of the Department of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans, and HOWARD MAHORNER, B.A., M.D., M.S. (Surgery), F.A.C.S., Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans. Pp. 147; 50 illustrations and 2 color plates. St. Louis: The C. V. Mosby Company, 1939. Price, $3.00.

Molding and Casting. Its Technic and Application. For Moulage Workers, Sculptors, Artists, Physicians, Dentists, Criminologists, Craftsmen, Pattern Makers and Architectural Modelers. By CARL DAME CLARKE, Associate Professor of Art as Applied to Medicine, University of Maryland School of Medicine. Pp. 308; 69 illustrations. Baltimore: The John D. Lucas Company, 1938. Price, $4.50.

Provoked Alimentary Hyperglycemia. The Mechanism of the Tolerance Test. By JOSEPH MARSHALL FLINT, Medical Clinic of the University of Lausanne. Pp. 37; 10 illustrations. *The Effect of the Macallum-Laughton Duodenal Extract upon Hypophyseal Diabetes.* By JOSEPH MARSHALL FLINT, and LOUIS MICHAUD, Medical Clinic of the University of Lausanne. Pp. 77; 14 illustrations. Lithoprinted by A. B. Macallum, London, Ontario, 1939.

League of Nations. Bulletin of the Health Organisation, Vol. 7, No. 6 (December, 1938). Pp. 163; 13 illustrations. New York: Columbia University Press, 1938. Price, 65c.

Pseudocyesis. By GEORGE DAVIS BIVIN, PH.D., and M. PAULINE KLINGER, M.A. (A Monograph of the George Davis Bivin Foundation.) Pp. 265; 5 plates and 18 tables. Bloomington, Indiana: The Principia Press, Inc., 1937.

"This monograph is the first attempt to bring together the widespread literature on a very interesting condition. The Principia Press is a company of scholars incorporated for the purpose of publishing meritorious works of learning. All profits are used for the endowment of books."

Medical Microbiology. By KENNETH L. BURDON, PH.B., SC.M., PH.D., Assistant Professor of Immunology and Bacteriology, Louisiana State University School of Medicine, New Orleans; Senior Visiting Pathologist, Charity Hospital of Louisiana at New Orleans, etc. Pp. 763; 120 illustrations. New York: The Macmillan Company, 1939. Price, $4.50.

The Massachusetts General Hospital. Its Development, 1900–1935. By FREDERIC A. WASHBURN, M.D., Director Emeritus. Pp. 643; illustrated. Boston: Houghton Mifflin Company, 1939. Price, $4.00.

Textbook of Pathology. A Correlation of Clinical Observations and Pathological Findings. By CHARLES W. DUVAL, Professor of Pathology and Bacteriology, Tulane University School of Medicine; Chief Visiting Pathologist, Charity Hospital, New Orleans, etc., and HERBERT J. SCHATTENBERG, M.D., Associate Professor of Pathology and Bacteriology, Tulane University School of Medicine; Visiting Pathologist, Charity Hospital, New Orleans. Pp. 681; 383 illustrations and 13 colored plates. New York: D. Appleton-Century Company, Inc., 1939. Price, $8.50.

The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds. By PERRIN H. LONG, M.D., Associate Professor of Medicine, The School of Medicine, The Johns Hopkins University; Associate Physician, The Johns Hopkins Hospital, etc., and ELEANOR A. BLISS, Sc. D., Fellow in Medicine, The School of Medicine, The Johns Hopkins University. Pp. 319; New York: The Macmillan Company, 1939. Price, $3.50.

NEW EDITIONS.

Medical Mussolini. By MORRIS A. BEALLE, Editor of Plain Talk Magazine. H. C. (CARLYLE) LOWRY, Technical Editor. Pp. 255; illustrated. Fifth Edition. Washington, D. C.: Columbia Publishing Company, 1939. Price, $3.00.

The aims of this book, but only a mild sample of its character, are to be found in the following quotation from the Preface: "The primary purpose of this book is to head off socialized medicine and its evils. Its secondary purpose is to point out the necessity of ridding the healing arts of the cancerous influence of the Medical Mussolini, and to grant every person the RIGHT to a doctor of his own choice and to the close personal relationship which should exist between the two. And thirdly, it would promote a private system of sickness insurance, instead of the bungling governmental operation of this sociological necessity." It contains a strange mixture of inaccuracies, ignorance, and leanings toward irregular practices, mixed with some ugly truths that require consideration by the discriminating physician. One cannot but regret that such an important subject is so inadequately handled or even suspect whether or not there is some concerted axe to grind. For revisions and additions to this edition, the author expresses indebtedness to the technical editor, H. C. ("Carlyle") Lowry.

Medical State Board Examinations. Topical Summaries and Answers. An Organized Review of Actual Questions given in Medical Licensing Examinations Throughout the United States. By HAROLD RYPINS, A.B., M.D., F.A.C.P., Secretary, New York State Board of Medical Examiners; Assistant Professor of Medicine, Albany Medical College, etc. Pp. 447. Fourth Edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, $4.50.

"This book is an expression of the writer's conviction that the average American medical graduate of today is well prepared for the practice of his profession and consequently that there is little basis for the obvious dread with which he approaches the ordeal of the licensing examination. It is based on fifteen years' experience as Secretary of the New York State Board of Medical Examiners. . . . After a critical survey of many thousands of questions actually used throughout the whole United States a selection of typical questions has been made and these immediately follow the review presented in each of the nine major medical subjects." (From the Author's Preface.)

Diseases of the Mouth and Their Treatment. A Text-book for Practitioners. By HERMANN PRINZ, A.M., D.D.S., M.D., D.Sc., DR. MED. DENT., Professor Emeritus of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania, Philadelphia, and SIGMUND S. GREENBAUM, B.S., M.D., F.A.C.P., Professor of Clinical Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania; Visiting Dermatologist, Mt. Sinai Hospital, Philadelphia General Hospital, Home of St. Michaels, and Eaglesville Sanatorium, etc. Pp. 670; 324 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $9.00.

Treatment by Diet. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago, etc. Pp. 691; 1 illustration. Fourth Edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, $5.00.

That a fourth edition has appeared since the first in 1934 proves that the book has achieved its purpose as a "simple, crystallized, practical and workable method of prescribing diets" in health and disease. New material includes chapters on Addison's disease and chronic hyperinsulinism, also extensive revision of the section on vitamins, and others.

Diseases of the Nose and Throat. By CHARLES J. IMPERATORI, M.D., F.A.C.S., Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc., and HERMAN J. BURMAN, M.D., F.A.C.S., Adjunct Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc. Pp. 726; 480 illustrations (some in color). Second Edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, $7.00.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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REGIONAL ILEITIS. A SUMMARY OF THE LITERATURE.

History. The description by Crohn, Ginzburg and Oppenheimer[52] in 1932 of the disease entity "terminal ileitis" focused a great deal of interest upon inflammatory lesions of the small bowel. Numerous surgeons began to report similar experiences. In retrospect, they recalled the confusing picture of a red, edematous terminal ileum complicating some of the appendices they had encountered at operation. They remembered that in an occasional case of so-called appendicitis, the symptoms had not been improved by the performance of an appendectomy, and that perhaps fistula formation and intestinal obstruction had appeared later on. Too, they recalled the case of intestinal tumor that, now and then, presented great difficulties of classification. Taking these data into consideration, and with their attention directed to this type of lesion, surgeons found that terminal ileitis was by no means a rarity, but a disease which they were recognizing more and more in their routine practice.

An investigation of the literature discloses much of interest on the subject of inflammatory intestinal growths. As early as 1806 Combe and Saunders[47] described what may well have been a case of regional ileitis under the title of "A Singular Case of Stricture and Thickening of the Ileum." Due to the fact that they included no microscopic study of the diseased portion of bowel, this cannot be substantiated with any measure of accuracy; but the gross pathologic description is suggestive.

In John Abercrombie's book, published in 1828,[2] the author presents a case in a girl of 13 years. The clinical history and gross pathologic

findings are quite compatible with a presumptive diagnosis of regional ileitis.

In 1882 Moore[181] for the first time gave a microscopic as well as a gross macroscopic description of a case of regional ileitis with intestinal obstruction in which a colostomy had been performed. The patient died because the colostomy opening was below the site of the obstruction. The author reports the absence of any tubercle bacilli or evidence of carcinoma, and states that the obstruction was due to "long-continued inflammatory changes."

No further mention of this condition is made in the literature until 1905, when Wilmanns[284] reported a case of intestinal obstruction following a chronic inflammatory thickening of the ileocecal valve, in which resection of the diseased segment of gut led to complete recovery.

In 1907, Moynihan[186] described simple inflammatory tumors of the large intestine, particularly of the sigmoid flexure, which simulated malignant disease. He furthermore called attention to the frequency of the condition, and attributed some of the cases of so-called cure after colectomy for carcinoma to this mimicry.

In 1908, Robson[224] stated that he had seen 5 cases, in an interval of 12 years, of inflammatory tumors of the large bowel which simulated malignancy.

Perhaps the most important contribution to the literature before the publication of Crohn's original article, was the paper by Braun,[29] in 1909, on inflammatory tumors of the intestinal tract. Prior to Braun's article this subject had gone unrecognized in German medical literature, with the exception of Wilmann's isolated case report. Braun reviewed the literature, discovering Moynihan's and Robson's communications. He further attached proper significance to these growths, and reiterated that they were often mistaken for carcinoma due to the fact that microscopic examinations had not been made. He also stated that these tumors had not occurred in the small bowel as far as he knew, and that they had no relation to the specific inflammatory tumors of syphilis, actinomycosis, or tuberculosis. Practically all of the literature dates from the appearance of this article.

Schmidt,[237] in 1911, recorded a case of a tumor involving the large bowel which was wrongly diagnosed preoperatively as carcinoma, but which proved to be an inflammatory growth upon study after resection. In the same year, von Bergmann,[273] in his paper on tumor formation in appendicitis, reported some 12 odd cases, several of which were probably regional ileitis.

A year later, Goto[101] listed 2 instances of simple chronic inflammatory strictures involving the terminal ileum and cecum which were misdiagnosed as malignancies. The same author reported 2 similar cases, 1 occurring in the transverse colon and extending as far as the beginning of the descending colon, and the other in the sigmoid flexure.

In 1913, Dalziel[57] published an excellent article in which he cited 4 cases of what he termed "chronic interstitial enteritis." Two of the cases involved the small intestine, 1 occurring in the mid ileum, the lesions in the other affecting over 2 feet of the jejunum. The disease process in the remaining 2 patients was confined to the large bowel, 1 being limited to the sigmoid flexure, and the other to the transverse

colon. Dalziel presented very accurate gross and microscopic descriptions of the resected portions of gut, and further recognized that some of these cases had been mistaken for hypertrophic intestinal tuberculosis. The author stresses the inadequacy of medical treatment and urges surgical intervention with resection of the diseased segment of gut as the recommended procedure.

Läwen,[162b] in his paper on fibroplastic appendicitis in 1914, advanced the theory that these inflammatory growths were due to extraordinary forms of chronic appendicitis. He ventured to say that the process began in the appendix and then spread to the cecum, ileum, and ascending colon. At the same time, he confirmed the impression of earlier authors that these processes had possibly been confused with hyperplastic intestinal tuberculosis, and proceeded to classify these growths as follows:

1. The inflammatory tumors of the cecum and adjacent ascending colon not having their origin in the appendix.

2. Inflammatory tumors which, to be sure, originate in the appendix, but only implicate this organ to a slight degree and extent either (*a*) into the anterior or posterior abdominal wall (inflammatory tumors of the abdominal wall after appendicitis, perityphlitic induration of the retroperitoneal tissues, etc.) or (*b*) into the surrounding intestine and omentum with the formation of connective tissue-like induration and conglomerated tumors (fibroplastic appendicitis in the broader sense).

3. Inflammatory tumors which originate in the appendix and which remain, in the main, localized to the appendix itself, the cecum, ascending colon and terminal ileum (fibroplastic appendicitis in the narrower sense, of idiopathic ileocecal tumor of appendicular origin).

In 1918, Jones and Eisenberg[134] reported another case of inflammatory tumor of the intestine simulating malignancy. In 1920, Tietze[264] published a comprehensive discussion of inflammatory tumors of the large intestine and included in his paper a very complete bibliography. Bachlechner,[10] in 1921, reported several cases of inflammatory ileocecal tumors in which he successfully resected the diseased portions of bowel. In 1922, Fröhlich[87] noted an interesting case of inflammatory growth involving the cecum in which the preoperative diagnosis had been a tumor of the adnexa. The following year, Moschcowitz and Wilensky[183] published the first comprehensive survey of non-specific intestinal granulomata in this country. They emphasized the non-specific origin of the disease and also the presence of foreign body giant cells, and commented on the remarkable resemblance of some of the cases to hyperplastic tuberculosis of the intestines. They furthermore reviewed the literature on the latter subject, and arrived at the conclusion that this form of tuberculosis was rather uncommon, and that many of the cases of so-called "hyperplastic tuberculosis of the colon" were in reality simple inflammatory processes. In the same year, Tenckhoff[262] and in the following year, Barth[17] reported on fibroplastic appendicitis and concurred with Läwen in the opinion expressed by the latter that these tumors were of appendicular origin.

In the ensuing years, many isolated reports of similar observations appeared in the literature. Horsley,[119] in 1925, described a case of typical regional ileitis. Metge,[175] in the same year, described a similar

process in the mid enteron, and analogous conditions were cited in Cabot[34] (Case 12133), in 1926. In this year also, there was reported a case by Markiewitz[171] involving the cecum. In 1927, Razzaboni[220] speculated as to the possibility of a virus as the etiologic agent of these growths. In 1928, Most[184] reported on inflammatory tumors of the stomach and ileocecal region, and in 1931 A. Fischer[80] also published a case of regional ileitis. The same year, Mock,[179] in a rather complete review of the literature, discussed infective granulomata in great detail and concluded that they comprised a definite pathologic entity. A year later, Golob[99] published an article on the same condition.

However, the importance of this disease process was not fully realized until 1932, when Crohn, Ginzburg and Oppenheimer published their observations. Since that time numerous articles of importance on the subject have found their way into the literature, and the original concepts of the disease have been considerably modified.

Etiology. Numerous authors have put forth different theories as to the causative factor involved in the production of this disease. So varied are the etiologic agents suggested, that coherence may be obtained only by grouping them in classes, the members of each category being characterized by some common factor.

1. Bacteria. Several bacteria have been implicated as the etiologic agent, but as yet there has been no conclusive evidence to establish any one organism as the sole cause of regional ileitis.

(*a*) *B. Coli.* Erb and Farmer[72] gathered some evidence which would seem to point to a member of the B. coli group as the etiologic factor. In a stained section of the involved portion of gut they found Gram-negative bacilli. They also isolated an organism from the ileal ulcers, the mesentery, regional lymph glands, liver and gall bladder, which proved to be B. coli or a close relative upon laboratory examination (culture obtained 8 hours postmortem; body kept in refrigerator in the interim). However, Erb and Farmer failed to perform agglutination tests with the patient's blood.

Ross[230] also found evidence of a similar character in a case which he encountered.

Numerous other investigators have failed to corroborate these findings and, although they may be interesting, they nevertheless represent isolated instances without proper controls and as such, are quite inconclusive.

(*b*) *B. Dysenteriæ.* Felsen has made repeated claims for this organism as the causative agent. This investigator has completed thorough clinical and laboratory studies and has come to the conclusion that there is a causal relationship between bacillary dysentery and regional ileitis. Bacillary dysentery, Felsen asserts, is not a stereotyped disease constantly involving the same portion of the intestinal tract, but rather a disease with protean manifestations, exhibiting itself in many bizarre forms. When it involves the terminal ileum in an acute inflammatory process it produces a red, thickened, boggy, edematous loop of bowel sharply demarcated from the adjacent normal tissue. There is also present an accompanying acute mesenteric lymphadenitis affecting the regional lymph nodes. In most cases the acute ileitis tends to subside, but some instances have been noted in which the condition progressed

to the chronic non-specific stage with fibrosis and stenosis of the intestinal lumen. Felsen has fairly consistently succeeded in obtaining cultures of B. dysenteriæ (Flexner or Sonne-Duval) in the acute stages of the disease. He states that, if the diagnosis is to be made, then early culture of the feces and repeated agglutination studies are necessary. It is Felsen's belief that B. dysenteriæ and the specific agglutination titre usually disappear in those patients in whom the acute lesions fail to heal, due to the complication of secondary non-specific infection. However, he cites an extremely interesting case with a history of regional ileitis of 10 years' duration, in which a resection was performed and bacteriophage and cultures were both positive for B. dysenteriæ.

In spite of these rather consistent findings, numerous other investigators employing thorough examinations, have failed repeatedly to recover B. dysenteriæ in one form or another. Hence, although this organism can and does undoubtedly produce a lesion resembling that in regional ileitis, nevertheless the claim of Felsen that it is the sole cause has not been established.

(*c*) *Tubercle Bacillus.* Due to the remarkable similarity in appearance between the chronic stage of regional ileitis and hyperplastic intestinal tuberculosis, it has been thought by some that the tubercle bacillus is the cause of both conditions. This similarity is further enhanced by the frequent appearance of giant cells in sections of diseased gut in regional ileitis. However, repeated sections stained for the tubercle bacillus have always been negative, as have countless guinea-pig inoculations. The tubercle bacillus may therefore be ruled out as the etiologic agent.

(*d*) *Mycobacterium Johnei.* Because of the gross resemblance of the lesions of Johne's disease in cattle to those of chronic regional ileitis, Williams[282] attempted to demonstrate some relationship between these two entities by injecting johnin subcutaneously into patients with regional ileitis and also into normal controls. However, there proved to be no demonstrable relationship.

(*e*) *Other Bacteria.* Konjetzny[149a] found Gram-positive cocci in the submucosa and in the exudate of the bowel of 1 patient. The identity of the organism was never determined and it is not unlikely that it was a secondary invader. Fischer and Lürmann[81] found enterococci in the stools, and Peters[205] likewise found enterococci, as well as Bacillus acidophilus. Mixter[177] isolated an anaërobic streptococcus from the peritoneal fluid, regional lymph nodes and ulcers in a patient with regional ileitis. Albrecht[4] isolated an organism similar bacteriologically to B. pestis from a case of ileitis with involvement of the cecum and ascending colon, as well. Halligan and Halligan[107] found Aërobacteria aërogenes in pure culture in the peritoneal fluid of a case of regional ileitis. The value of this cannot be estimated since there was free perforation into the peritoneal cavity, and the organism may have come from the intestine.

Again, these are observations which are of interest, but which fail to give a clue as to the exact etiology of the disease due to their wide variability and lack of consistency. For the most part, although numerous attempts have been made to recover and identify organisms by anaërobic as well as aërobic cultural methods, by various staining

technique and animal inoculation, the vast majority of these efforts have failed. As Pumphrey[215] has well stated, in cases where it could be reasonably assumed that the specimens were obtained without fecal contamination, there was commonly no growth of a bacterium.

2. Bacterial Toxins. Erdmann and Burt[73] believe that the course of events in regional ileitis is somewhat as follows: A break in the mucosal continuity of the intestine occurs due to the presence of certain toxins. Subsequent to this mucosal ulceration, active infection ensues and makes its way into the wall of the bowel, producing here a low-grade inflammatory reaction characterized by cellular infiltration and connective tissue proliferation. This tenet seems quite unlikely, since similar lesions have not been encountered in other conditions in which mucosal ulceration exists.

3. Viruses. Razzaboni[220] described a case of regional ileitis in which numerous eosinophils were present in the sections of the diseased portion of the bowel. The patient also had an anemia, and the author suggests the possibility of a virus infection as the etiologic factor. Stafford[252] also suggests the possibility of a virus infection as the cause of regional ileitis because of certain similarities in the clinical course, and to a lesser extent, in the pathologic picture between regional ileitis and lymphogranuloma of the intestine, the latter a known virus disease. At present, however, there is no real evidence in support of this theory.

4. Protozoa. The Entamœba histolytica has been considered by some, notably Corr and Boeck,[49] as a possible cause of the disease. These investigators described a case in which amebiasis as the cause of the lesions was repeatedly suggested during the clinical course of the disease. Entamœba histolytica had been recovered from the stools at various intervals during the 7 years' duration of this disease in their patient. At autopsy, the pathologist called attention to "the undermined edges of the ulcerations" as indicating amebic infection. However, various other findings were listed by the authors as being contradictory to amebic etiology: (*a*) The colon and lower ileum were practically uninvolved; (*b*) the stenotic lesion and the hypertrophic polypoid growths are not characteristic of amebic infection; (*c*) amebic dysentery does not extend into the upper ileum as it did in this case (distal 5 inches of ileum were uninvolved, but the rest of the small intestine with the exception of the proximal 3 inches was marked by ulceration and polypoid masses); (*d*) there was no pus or blood in the diarrhea.

Other investigators have failed to find the Entamœba histolytica in countless stool examinations of numerous cases of regional ileitis. It is not unlikely, as Corr and Boeck suggest, that this organism was a secondary invader in their case, and that the amebiasis had been cleared up with proper treatment, but the regional ileitis had failed to respond to medical therapy.

5. Metazoa. Many writers, especially in Europe and Asia, have described inflammatory growths of the large intestines produced by Trichocephalus, Oxyuris vermicularis, Giardia lamblia and other parasites.[12,264] Recently, Barbour and Stokes[12] described an interesting case in a medical missionary with a history of alimentary infection by Entamœba histolytica, B. typhosus, B. paratyphosus and Giardia

lamblia. They ruled out Entamœba histolytica as playing a rôle in the etiology of the present disease because of the involvement of small intestine alone. Likewise, they excluded B. typhosus and B. paratyphosus due to the widespread pathologic changes in the small bowel (throughout the small intestine there were 13 inflammatory portions, the first being 21 inches from the pylorus and the last $4\frac{1}{2}$ inches from the ileocecal valve). Due to the fact that the Giardia infection was present up to the time of death and Giardia cysts were repeatedly recovered from the stools, the authors implicated this parasite as the primary cause of the lesions. Obviously, it is difficult to estimate the importance of these findings due to the numerous complications.

Although these parasites can produce a lesion greatly resembling regional ileitis, they cannot be regarded as the usual etiologic agent in view of the fact that repeated stool examinations in nearly all the cases of regional ileitis have failed to disclose the presence of any of the metazoan worms.

6. Achylia Gastrica. Nuboer[192] places etiologic significance upon Achylia gastrica because of the occurrence of this condition in some of the cases of regional ileitis that came under his observation. He claims that, due to the absence of the disinfectant power of the HCl and gastric juice, the microbes multiply and penetrate the intestinal wall. This is probably only a coincidental finding since the vast majority of the cases of regional ileitis have normal HCl and gastric juice present.

7. Allergy. Kovacs[151] mentions the possibility of allergy playing a rôle in the etiology of this disease. Kaijser[136] described 2 cases of almost identical nature in which there were allergic reactions in the small intestine following intravenous neosalvarsan injections. In both instances the abdomen was opened, and the gross findings resembled those encountered in acute regional ileitis. Kaijser suggests that many cases of so-called localized ileitis are possibly allergic bowel manifestations. Likewise, Cassirer[38] cites a patient of Harrington, who on account of severe abdominal pain with simultaneous Quincke's edema was operated on and a "thickened and contracted" segment 6 cm. long was found in the lower ileum. Kraemer[152] calls attention to the prominent enlargement of the regional mesenteric lymph nodes in regional ileitis, and suggests that possibly the disease is primary in the lymph nodes with a secondary allergic spread to the intestine by way of the mesenteric lymphatics due to an overwhelming dose of infective agent.

As yet, there is no substantial evidence to support the allergic hypothesis as the etiologic factor in the production of regional ileitis.

8. Foreign Bodies. Foreign bodies have been implicated by many as the cause of non-specific inflammatory intestinal granulomata. Jaffe[125] reported a case in which a fish bone was found. Tietze[264] noted an instance of cecal granuloma following appendectomy in which the silk thread used to ligate the appendix was discovered. Schreiber[239] listed a case of ileocecal granuloma containing numerous plum and cherry pits. Morian[182] and Jaffe[125] recorded the finding of a piece of bone in a granuloma of the colon.

While a foreign body may undoubtedly produce a non-specific inflammatory growth in the intestine, this is obviously not the ordinary etio-

logic agent, since in the great majority of cases of regional ileitis, diligent search has failed to reveal the presence of foreign bodies.

9. Trauma. Pupini[216] reported a case of stenosis of the small bowel due to trauma. The patient suffered a severe blow at the level of the umbilicus, which caused immediate intense pain. Operation 2 months later revealed a 10 cm. segment of the middle ileum with an intensely hyperemic serosa, infiltration of the muscle walls resulting in a rigid thick tube, and also an annular stenosis of the intestine in the involved region.

Reichert and Mathes[222] reported a similar case.

Leonardo[164] published a case in which the terminal ileum, cecum, and ascending colon were the site of a non-specific granuloma. The cause of the disease he attributed to secondary infection due to slight trauma to the ileocecal region in the course of a previous "Robbin operation" for an adherent retrocecal appendix, through a small gridiron incision.

These, too, are the exception rather than the rule and cannot be interpreted as the sequence of events in the ordinary case of regional ileitis.

10. Non-specific Inflammation of the Appendix. As early as 1914, Läwen[162b] cited cases of intestinal non-specific granulomata involving the ileocecal region which he thought were due to an extraordinary form of chronic appendicitis called fibroplastic appendicitis. He interpreted this process as starting in the appendix and spreading to the cecum, ileum and sometimes the ascending colon. In this same article he reports cases of tumor formation which were described by von Bergmann in 1911. Although it cannot be stated with certainty, probably some of the cases listed by von Bergmann[273] were instances of regional ileitis. Bachlechner, in 1921, also indicated a belief that the appendix might be the offender in some of these cases. Tenckhoff,[262] Barth,[17] and Zwerg[289] described similar processes. Fischer[80] claims that possibly the changes in the ileum and mesentery are secondary to chronic mesenteric lymphadenitis which results from an appendicitis, the latter condition being capable of healing. Kapel,[140] however, denies this, stating that in too many cases the mesentery is found to be normal. More recently, Ravdin and Rhoads[219] have pointed out the similar pathologic pictures in fibroplastic appendicitis and the chronic stages of regional ileitis.

It is interesting to note that many of the patients who come to operation with regional ileitis have had previous appendectomies. The intervals between these operations have varied from a few weeks to many years. However, it seems unlikely that the appendectomy which often preceded the symptoms and signs of regional ileitis by a number of years could be closely related to the latter. Especially is this so in the light of the fact that the inflammatory granuloma often occurs at quite a distance from the appendix. Too, in many patients with regional ileitis, the performance of an appendectomy fails to relieve the symptoms and often leads to fistula formation. Hence, while appendicitis may sometimes play the rôle of an etiologic agent, nevertheless, the finding in numerous cases of regional ileitis of an appendix grossly and microscopically normal precludes the implication of this organ as the usual primary seat of the pathologic process.

11. Impairment of the Blood Supply. An impairment to the blood supply of the gut has been followed by granulomatous changes in the area supplied by the affected vessel. Such lesions have been encountered following intestinal obstruction, recurrent partial volvulus, mesenteric thrombosis, hernial incarceration and intussusception. In these cases, vascularization through collateral channels is ample to ward off necrosis of the muscular and fibrous layers of the gut. Ginzburg and Oppenheimer[94] state that such vascularization is not adequate for the mucosa to regenerate to any extent. As a result, ulcerations of the mucosa occur and secondary infection sets in, followed by connective tissue proliferation producing stenosis of the bowel lumen. These authors find the final picture in such instances analogous to that produced in regional ileitis.

Bockus and Lee[26] discuss the possibility of some peculiarity of the anatomy in the terminal ileum, its mesentery and blood supply as contributing to the formation of an inflammatory mass. Quoting Batson, who states that the terminal branch of the ileocolic artery supplying the terminal ileal segment may undergo a good deal of rotation, they conceive of the possibility of this vessel being twisted or pinched by an extraordinary mobility of the terminal ileum, leading to the pathologic changes characteristic of regional ileitis. This, however, would presumably not apply to similar lesions occurring elsewhere in the intestinal tract.

DeCourcy[60] described a case of regional ileitis in which he felt that he "was dealing with a thrombus of the small terminal vessels of the gut wall with inflammatory extension in both directions along the layers of the bowel." He concluded that if this was true, then possibly ileitis was not a distinct pathologic entity but a complication which might take place anywhere in the intestines.

Bell,[20] however, in an experimental study dealing with interference of the blood supply to the gut, was not able to produce a granulomatous lesion, ulceration of the mucosa, or any other lesion resembling those in regional ileitis, and concluded that the pathologic changes in this disease were not due to inadequate blood supply.

12. Interference with the Lymphatic Supply. Bell[20] also speculated as to whether the etiologic agent might be mucosal infection spreading to the wall of the intestines and producing edema of the mesentery due to insufficient lymphatic drainage, or whether the infection began as a lymphangitis and then involved the wall of the gut.

More recently, Reichert and Mathes[222] described a series of experiments in which they produced chronic lymphedema of the ileum and colon by injections into the mesenteric and subserosal lymphatic vessels of various sclerosing materials. Employing the intravenous injection of bacteria together with the lymphatic sclerosing preparations, they were able to produce edema and extreme thickening of the wall of the bowel, which changes seemed to be permanent. Reichert and Mathes believe that regional ileitis is characterized by a low-grade chronic lymphatic infection with an accompanying chronic lymphedema. The greater severity of the pathologic changes in regional ileitis as compared with the experimental results, they attribute to the persistence of a chronic low-grade bacterial infection. The observa-

tions of Homans, Drinker, and Field[118] that the streptococcus may produce lymphatic obstruction resulting in lymphedema of the lower extremities lend credence to the work of Reichert and Mathes.

13. HEREDITY. Crohn[51c] reported a case of familial incidence of regional ileitis occurring in a brother and sister. He stated that this might be accidental or due to a congenital predisposition or transmissible etiologic factor. However, in light of the lack of evidence and corroboration by others, it is very likely that the former assumption is the correct one.

Since all these various etiologic factors may produce lesions which greatly resemble one another, one must, in the absence of further proof, think of the possibility of regional ileitis resulting from a number of heterogeneous primary irritating agents.

Symptomatology and Clinical Course. The symptoms vary with the location of the lesion and the stage of the disease encountered. Crohn, in his original paper, divided the symptoms into four groups:

1. *Signs of "Acute Surgical Abdomen."* These patients exhibit the symptomatology of an acute intra-abdominal inflammation which cannot be distinguished preoperatively from acute appendicitis. Pain and tenderness are present in the right lower quadrant (if the terminal ileum be involved; pain is higher up if the lesion is in the upper ileum or jejunum) accompanied by generalized colic, fever (up to 103° F.), and a moderate leukocytosis. A mass may be palpable. At operation it is readily seen that the involved segment of intestine is soggy, edematous, reddened, and greatly thickened. The mesentery of this portion of the bowel is also edematous and thickened, and contains numerous large, succulent, hyperplastic lymph nodes. There may be a small amount of clear fluid present in the abdominal cavity. The appendix most commonly shows little sign of pathologic involvement such as mucosal ulceration, but may be slightly reddened due to its proximity if the granulomatous lesion be in the terminal ileum or cecum. Occasionally, the appendix is seriously diseased as revealed by gross and microscopic study. Indeed, an abscess may be found. Attempted drainage may lead to the formation of a chronic intractable fistula after operation.

2. *Symptoms of Ulcerative Enteritis.* These patients have colicky abdominal pain, a low-grade diarrhea with stools containing mucus and blood, but no grossly visible melena. There is also found malaise, marked weight loss and a secondary anemia. This anemia may become very severe as the disease progresses, and the patient may suffer a marked loss of strength. Rarely is tenesmus seen, and the gripping at stool and urgency characteristic of colitis and rectal disease are absent. Moderate fever, intermittent in type, is commonly seen, there being periods during which the patient is apyrexic.

3. *Symptoms of Chronic Incomplete Intestinal Obstruction.* The stage of ulceration is followed by the stenotic phase. However, the latter may appear with or without the patient having experienced the symptoms of one of the previous stages, for occasionally the first indication of the disease may be the signs of incomplete intestinal obstruction. This obstruction is due to the extreme thickening of the wall of the

intestine with resulting narrowing of the intestinal lumen. Severe abdominal cramps, borborygmus and visible peristalsis are the chief complaints. The pain may be temporarily relieved by defecation, only to return a short while later. There may be vomiting which is, however, usually intermittent in type and is not that of impending obstruction. A mass is usually present in the lower right abdomen since the terminal ileum is most commonly the site of the disease. However, with upper ileal or jejunal involvement, the mass may be higher up in the abdomen. Not uncommonly the mass may be palpated in the left lower quadrant in those cases in which there are adhesions and fistulous communications with the sigmoid.

4. *Chronic Fistula Formation.* These fistulas occur very late in the disease and have formed as a result of the slow perforation of the ulcers, or following drainage of an intra-abdominal abscess. In the latter instance, they may occur months after the original drainage operation for a supposed appendiceal abscess. In contradistinction to fistulas of appendicular origin which tend to heal, these fistulas fail to close spontaneously, and resist simple operative closure by excision and inversion of the stump. These fistulas are of various types: (*a*) Internal—from the ileum, or involved segment of bowel to any of the surrounding hollow viscera, particularly to the sigmoid, cecum, transverse colon, rectum, vagina, uterus. (*b*) External—from the ileum, or involved segment of bowel to the abdominal wall, invariably following the line of scars of previous operations. These fistulas, when appearing and perishing after an appendectomy for a supposed acute appendicitis has been performed, are almost diagnostic of regional ileitis. (*c*) Fistulo-in-ano—Crohn[54a] states that 15% of all cases of regional ileitis are accompanied by perirectal abscesses or perianal fistulas, which may occasionally be one of the earliest manifestations of the disease.

Roentgen Findings. Although the diagnosis may be suspected clinically, nevertheless, it cannot be established with certainty unless a roentgenologic examination be done. Satisfactory Roentgen examination of the small intestine may be accomplished by the following methods. A barium sulphate enema is given under roentgenoscopic control until the terminal ileum is filled by reflux through the ileocecal valve. The large intestine is then emptied by defecation and the ileum remains filled with the contrast fluid. Although satisfactory for the terminal ileum, this procedure is obviously unsatisfactory for lesions higher up in the small intestines. The upper segments of small intestine may be studied by following the progress of a simple mixture of barium sulphate and water through the segments, as recommended by Kantor.[139] The standard opaque meal is given on an empty stomach and all the films are taken with the patient prone. In this position the ileac loops are more widely separated. Observations are made at intervals of 1 hour from the time immediately prior to cecal filling until the normal time of ileac emptying (3 to 9 hours after ingestion of the opaque meal). Changes may be found anywhere in the small intestine from the jejunum to the ileocecal valve, and also in the large intestines. The changes in the colon may either be spasm secondary to ileal involvement, or else the large bowel may itself be involved in the pathologic

process. In the former case, the spasm is intermittent and the barium meal generally fills out the affected areas in normal contour. Kantor describes the following signs:

1. In the early stages of the disease there is found an absence of variation in the diameter of the intestinal lumen, signifying rigidity. As the disease progresses, there is seen a constant filling defect in the affected loop of bowel. The degree of this filling defect depends upon the extent of the stenosis present.

2. The loops of intestine proximal to the filling defect may be abnormal in contour, being irregular in shape.

3. If actual obstruction is present there is stasis and dilatation of the loops proximal to the filling defect. If the lesion occurs in the ileum the stasis may be 9 hours or more after the opaque meal.

4. The "string sign"—a thin, irregular linear shadow which suggests a cotton string and thereby derives its name. This represents the thinned-out barium filling of a greatly narrowed intestinal lumen. It extends throughout the entire region of the filling defect. Weber has proposed the term "twisted cord appearance" as an alternative for "string sign." While it is highly suggestive, this "string sign" is not pathognomonic, and its absence does not exclude regional ileitis. The string sign may be present in other stenosing processes, and has been observed in sarcomas and in syphilis of the terminal ileum. Kantor has pointed out the roentgenologic criteria for differential diagnosis from a filled appendix, tuberculoma, stenosing sarcoma, intestinal syphilis, the line of the right sacroiliac synchondrosis, and normal ileal spasm without organic lesion.

Pathologic Anatomy. In the early acute stage of the disease, the affected portion of the intestine is a blotchy, soggy, edematous mass, greatly thickened and reddened. Its mesentery is also thickened and edematous and contains numerous large hyperplastic glands. The serosa presents a mottled red appearance and often there is found a small amount of serous fluid in the peritoneal cavity. The mucosa may show ulcerations, particularly along the mesenteric border of the bowel. Microscopically, the mucosal ulcerations may be seen to be covered with a layer of fibrinopurulent exudate. The wall of the intestine is also invaded by the acute inflammatory reaction which tends to decrease in severity as the subserosa is reached. The latter is the site of edema, congestion and interstitial hemorrhage but, in contrast to the submucosa, usually does not have many neutrophils. The entire bowel wall, then, is infiltrated by an acute inflammatory granulation tissue.

In the later stages of regional ileitis the pathologic changes have become more advanced. The diseased gut presents the appearance of a thick, firm, rigid, unyielding tube, not unlike a garden hose. Its mesentery is likewise greatly thickened, sometimes to the extent of $\frac{3}{4}$ inch. There is a marked tendency toward perforation, which is combated by the formation of adhesions to the parietal peritoneum, the omentum or adjacent viscera. As a result, when ulceration through all the intestinal layers takes place, the contents of the bowel are not usually discharged into the peritoneal cavity, but either onto the surface of or into another organ. In Crohn's original series of cases, free perforation into the peritoneal cavity had not been noted. Since that

time, however, Arnheim[8] and Jackson[123] have described cases with free perforation and resulting peritonitis. Also, Halligan and Halligan[107] have recorded another instance of perforation, the perforation having been the first sign of regional ileitis. These, however, are the exception rather than the rule (being the only cases of free perforation in the literature). The more usual occurrence is a chronic process with the cavity tending to be walled off by adhesions. The earliest perforations take the form of linear fistulas that have their origin in mucosal ulcerations on the mesenteric border of the intestine, which penetrate the intestinal wall to the subserosa. As the severity of the ulcerations increase and perforation of the sinuses through the wall of the gut occurs, they may lead to the formation of an abscess in the mesentery. If the disease process affects the terminal ileum, this region is usually more involved at the ileocecal valve and the lesions taper off in degree as one proceeds proximally. Very commonly, the diseased segment is sharply demarcated from the normal intestine. The lumen of the bowel is greatly constricted and distorted, sometimes being almost completely obliterated. Often, the loop of intestine proximal to the stenotic segment is greatly dilated. The mucosa is swollen and shows a series of ulcerations on the mesenteric border. Crohn,[52] in his original article, was uncertain as to whether these ulcerations were the vestiges of the original ulcerative lesions, or the result of shortening of the diseased mesentery, but now believes the former to be the case. The normal intestinal folds are in part destroyed and in part broken up into polypoid masses, and not uncommonly into papillary excrescences. The serosa is thickened and fibrosed, and frequently presents small tubercle-like structures on its surface. It is these which have caused so much confusion and faulty diagnosis at the operating table, leading the surgeon to call the simple granulomatous lesions "hyperplastic tuberculosis of the intestines."

Histologic sections confirm the gross thickening of the intestinal wall. Closer study reveals this thickening to be due partly to hypertrophy of the muscular layer, and partly to an extensive inflammatory process that involves the submucosa, muscularis and subserosal layers with varying amounts of fibrosis. The submucosa also is usually greatly thickened. The mucosa presents various changes. Sometimes the entire mucosa has become eroded; in other instances only the surface epithelium has been destroyed. There are irregular ulcerations lined by a non-specific granulation tissue containing many neutrophils. The mucosa also shows some areas of atrophy and other zones of polypoid hyperplasia. A chronic, non-specific granulation tissue extends diffusely throughout the muscular layer and into the subserosa. This granulation tissue contains nodules or granulomas composed of fibroblasts and histiocytes, and very commonly, of foreign body giant cells. Some believe that these giant cells have resulted from an inflammatory reaction around inclusion particles of non-absorbable vegetable matter which have come to lie at the base of the ulcers and have been entrapped when healing occurred. These observers believe it not unlikely that the vegetable cells possibly contribute to the hyperplastic fibrosis by virtue of their irritant action. However, Pemberton[202] states that the giant cell reaction is analogous to that which can be experimentally

produced by injecting animal oils and is a response to a lipoid substance. These giant cells are indistinguishable from the Langhan's type. Dense aggregates may occasionally be present and strongly suggest tubercles. However, Ziehl-Neelson stains, done with a positive control, fail to bring out an acid-fast bacillus. It is interesting to note the position of the giant cells in the case reported by Barbour and Stokes.[12] Here they were restricted to the intermuscular plans and were in close juxtaposition to Auerbach's plexus. These authors suggest that the involvement of Auerbach's plexus may account for the ballooning of portions of the gut which was present in their patient.

Differential Diagnosis. It is important that regional ileitis be differentiated from a number of conditions which may mimic it both in symptomatology and, not infrequently, in gross appearance at operation.

1. *Neoplasms.* Sarcoma and carcinoma of the intestine may simulate regional ileitis surprisingly. So much is this so, that the diagnosis of inoperable carcinoma has been made at the operating table in numerous instances of regional ileitis, and the true condition remained unrevealed until microscopic study of the diseased bowel had been completed. However, as Wakely[275] pointed out, carcinoma of the jejunum and ileum is a very rare condition indeed. Sarcoma of the intestines is also uncommon and rarely causes stricture, but when it does, gross differentiation from regional ileitis may indeed be difficult. Biopsy of a regional lymph node or histologic study of a section of the diseased bowel, in these cases, will aid in the diagnosis.

2. *Hyperplastic Intestinal Tuberculosis.* Ulcerative intestinal tuberculosis occurring secondary to pulmonary involvement is by no means uncommon, and very frequently occurs in patients with active pulmonary lesions. This type of intestinal tuberculosis is characterized by the presence of ulcerated lesions scattered throughout the jejunum and ileum, and to a lesser degree in the colon. These ulcers lie more or less in the transverse axis of the bowel, and the serosal tubercles on the external surface give one a means of identifying the lesions.

On the contrary, hyperplastic intestinal tuberculosis of the ileum alone is almost never seen, as Dowdie points out, there having been only 8 cases reported in the literature up to 1931. This condition may or may not be associated with pulmonary tuberculosis, but is usually thought to be a primary lesion because of the failure to find tuberculous infection anywhere else in the body, and also because of the cure produced by resection of the diseased section of intestine. Undoubtedly many cases of regional ileitis have been falsely labeled as chronic hypertrophic intestinal tuberculosis due to the gross and microscopic similarity of the two conditions. The former may present tubercles not of the exact type seen in tuberculosis; there are also quite frequently found in regional ileitis giant cells of the Langhan's type. Final differentiation may be made by guinea-pig inoculation and by staining of the sections of intestine for tubercle bacilli. In all instances of regional ileitis both of these procedures have consistently yielded negative results.

3. *Ulcerative Colitis.* A very important differentiation is that which must be established between regional ileitis and non-specific ulcerative colitis. In most cases, colitis may be recognized by roentgenologic

studies with the opaque barium enema and also by sigmoidoscopy. However, in those forms of colitis involving only the proximal portions of the colon in which there are no lesions of the sigmoid and rectum, differentiation is quite difficult. These cases may be recognized by the spasm deformity of the portions of the colon involved and by the obliteration of the haustra. Clinical differentiation is usually not possible, the final diagnosis being on a roentgenologic basis. Colitis does not usually produce fistulas except in the anal and rectal regions. Also, in colitis, one rarely encounters a palpable mass.

In cases of regional ileitis with colonic involvement there is clinically a slight diarrhea, high temperature, much prostration and abdominal tenderness. In contradistinction to this, a severe colitis with ileal "wash-back" may represent a terminal stage of an intractable colitis with probably 20 to 30 stools a day.

4. *Actinomycosis.* The intestinal form of this disease usually originates in the cecum and frequently results in the formation of a mass in the right lower quadrant. However, this disease is extremely rare both in this portion of the body, and in the United States. The diagnosis is based on the presence of the characteristic yellow "sulphur" granules in the discharge.

5. *Syphilis.* Syphilis of the intestine, although uncommon, may occur both as a congenital and as a primary condition. In the former, the lesions are found most often in the terminal ileum, where the healing of the syphilitic ulceration produces constriction and stenosis. Primary syphilis of the intestine has a predilection for the lower end of the colon and rectum and thus offers no differential diagnostic problem.

MacCollum[169] states that tertiary lesions of the small intestine are usually localized in the jejunum or upper ileum where they appear as flat elevations involving the mucosa and submucosa. Annular strictures may occur at these sites due to the healing of multiple ulcers. Because of the comparative infrequency of this condition and the aid given by the history of syphilitic infection and positive serologic data, this disease should not offer much difficulty in differential diagnosis.

6. *Hodgkin's Disease.* This disease may be differentiated from regional ileitis by histologic examination of a regional lymph node, which will then disclose the typical pleomorphic cellular character of the lesion.

7. *Appendicitis.* In the acute stages it is usually impossible to differentiate regional ileitis from acute appendicitis preoperatively. The diagnosis in these cases can only be made at the operating table. However, Crohn[51a] has recently called attention to diarrhea as a differentiating symptom between acute regional ileitis and acute appendicitis, the latter condition rarely being accompanied by diarrhea. The above author believes that diarrhea should always arouse the suspicion of acute regional ileitis.

8. *Other Lesions.* Regional ileitis has also, in rare cases, simulated chronic intussusception,[32] and twisted ovarian pedicle and cyst.[54] It must also be differentiated from mesenteric lymphadenitis,[225] postoperative adhesions,[50,128,238] appendiceal and periappendicular abscess,[111,229,116,7,212,132] tuboövarian tumors, cysts, inflammations and abscesses,[176b,138,87,123] Meckel's diverticulum tumor, cyst, inflammation

or strangulation through its rudimentary band,[140] and localized idiopathic dilatation of the ileum. Final differentiation is again on a roentgenologic basis.

Statistical Summary and Analysis. Of a total of 393 cases in the literature in which the sex was specified, 222 (56.6%) occurred in male patients and 171 (43.5%) in females. Although males predominate over females to some extent, nevertheless the proportion of incidence of regional ileitis is not in the ratio of 2 to 1 as Crohn stated in his original description.

TABLE 1.—SUMMARY OF AGE GROUPS OF CASES OF REGIONAL ILEITIS.

Age group.	No. of cases.	Per cent.
1–10	18	4.7
11–20	68	17.8
21–30	140	36.6
31–40	76	19.9
41–50	40	10.4
51–60	24	6.2
61–70	13	3.4
71–80	3	0.8

Of a total number of 413 cases in the literature with available data concerning previous abdominal operations, 112 (27.1%) have had previous appendectomies performed.

TABLE 2.—SUMMARY OF SITE OF LESIONS.

Region of intestine involved.	No. of cases.
Terminal ileum	261
Terminal ileum and cecum	80
Terminal ileum, cecum and ascending colon	20
Terminal ileum, cecum, asc. colon and transverse colon	1
Terminal ileum and colon	6
Terminal ileum and lower jejunum	2
Jejunum	16
Terminal jejunum and upper ileum	1
Upper ileum	5
Scattered involvement of ileum	1
Entire ileum	1
Mid ileum	13
Ileum (exact location not specified)	29
Entire small intestine (beginning with jejunum)	2
Terminal duodenum and proximal jejunum	2
Cecum	10
Cecum and ascending colon	7
Cecum, ascending colon and transverse colon	1
Ascending colon	4

The author has attempted to include in the group entitled complete recovery only those cases which have had a minimum follow-up of 1 year, during which period there have been no signs or symptoms of regional ileitis after operation. It is realized that such an arbitary standard is inadequate because some of the cases reported as complete cures may turn up later as recurrences. However, some such standard is necessary for statistical purposes and a follow-up of 2 to 3 months is of little value. On the other hand, the subject is so recent that there are insufficient 5-year follow-ups.

Treatment. The treatment depends upon the stage of the disease and the condition of the patient. In the acute stage of regional ileitis, there is no unanimity of opinion as to the surgical procedure of choice. A considerable number of observers recommend radical surgery in the acute stage (enterostomy, resection, short-circuiting) because of the frequently progressive character of the disease.[15,23,25,46a,49,90,94,111,145a,165,177,211] On the other hand, the more recent tendency has, for the most part, been toward a conservative mode of therapy. By conservative treatment is meant an exploratory laparotomy with no operation on the

TABLE 3.—SUMMARY OF OPERATIVE PROCEDURES EMPLOYED AND RESULTS.

Type of procedure.	Total number of cases.	Complete recovery.	Partial recovery.	No improvement.	Recurrence.	Deaths.	Too recent to evaluate recovery or no adequate follow-up.	Remarks.
Resection	290	197 (67.9%)	17 (5.8%)	11 (3.8%)	18 (6.2%)	21* (7.2%)	23	1 died 2 yrs. postop. of cirrhosis seen at op.; no sympt. of ileitis postop.;[207] 1 well for 3 mos. postop.; died 4 mos. postop. of perf.-aut. rev. severe ileocolitis;[231] 2 dev. acute int. obst. 1 mo. postop. due to fibrous band constr. ileum; div. of band led to compl. rec.[39,134]
Short-circuiting	88	27 (30.6%)	10 (11.3%)	5 (5.7%)	26 (28.4%)	7* (7.9%)	14	3 dev. pern. anem. postop.; 1 devel. beriberi.[232]
Appendectomy	70	39 (55.5%)	2 (2.9%)	8 (11.4%)	6 (8.6%)	3 (4.3%)	12	1 died 2 mos. postop. of meningitis without abd. sympt. —aut. ref.[104]
Exploratory laparotomy	24	2	2	5	1	9	5	9 were of acute type res. in 3 deaths, 2 compl. recov., 1 part. recov.; 3 too recent to evaluate.
Enterostomy	16	6	..	5	1	3	1	
Resection and enterostomy	12	6	2	1	1	2		
Drainage of abscess	5	..	1	3	..	..	1	
Closure of perforation	1	1	..	..	..	..	..	Acute free perforation.[107]
Separation of adhesions and closure of perforation	1	..	..	..	..	..	1	

* 3 deaths in Dixon's series[65] of 2-stage resections and short-circuiting operations are not listed in either group separately.

intestine *per se*, or exploration and appendectomy. In the latter instance, it is assumed that the possible resolution of the disease occurs spontaneously, and not as the result of the appendectomy which is regarded as being incidental. The conservative approach was recommended by Meyer and Rosi[176b] and has since been adopted by numerous others, including Crohn.[16,31,51a,150,163,170] Meyer and Rosi feel that resec-

tion may be unnecessary if the disease is limited to the terminal ileum and the mesentery is not involved, since they believe that spontaneous resolution may occur in these cases. However, if the mesentery is also attacked by the disease process and is thickened and edematous, then spontaneous resolution is less likely to occur.

There is a fair number of cases in the literature in which spontaneous resolution following an exploratory laparotomy or exploration and appendectomy has occurred.[23,24,31,72,78,95,150,156,163,176b,212,213,225,242,257,287] Furthermore, there is roentgenologic evidence that spontaneous resolution may occur.[53,176b,278] In addition, there is direct evidence at the operating table that resolution is possible. Pessagno[204] has reported an interesting case in which primary resection was followed by recurrence in a previously healthy portion of intestine. At the final of several operations which was done to repair an enterostomy fistula, large segments of intestine previously seen to have been diseased were apparently normal.

On the other hand, a large number of cases which had been treated conservatively progressed to the chronic stage of the disease. This group is probably larger than would be indicated by a casual inspection, since, in many cases, the appendectomies were not performed by the surgeon reporting the case, and the presence of regional ileitis at the time of appendectomy is unknown. Furthermore, because of the slow progress of the disease, many of the individual reports cannot be evaluated properly due to the lack of adequate postoperative observation. Hence, one does not accurately know how many of the acute cases treated conservatively remain well indefinitely, and how many gradually progress into the chronic stages of the disease.

However, because of the definite possibility of spontaneous resolution in the acute stage, conservatism should be the rule. If the symptoms persist, or if recurrence takes place, then a radical operation can be performed later. Furthermore, the risk in the latter instance will probably be less, because resection will no longer be an unexpected emergency procedure undertaken upon a patient who is not properly prepared. Needless to state, repeated careful observation is necessary in the patient in whom a conservative operation has been performed.

In the chronic stages of the disease, surgical treatment is undoubtedly the sole procedure to be recommended. Berg,[21] who has perhaps had more experience in this field than anyone else, advises a wide resection of the diseased segment of bowel, the extent of the resection being determined by the amount of lymphadenopathy. When the disease is confined to the terminal ileum, he recommends a wide resection of the latter together with the cecum and ascending colon, and an anastomosis between the remaining ileum and the transverse colon. Mixter and Starr,[178] and many others, believe that an important measure in preventing recurrence is wide excision of the diseased mesentery and its lymph nodes. Mixter[177] also emphasizes the fact that drainage should be avoided whenever possible in order to minimize the danger of fistula formation.

Dixon[66] is of the opinion that an ileocolostomy is to be utilized if the condition of the patient is poor, subsequent resection depending on whether the symptoms disappear or recur. Short-circuiting operations

have completely relieved the symptoms in only 30.6% of the patients in whom this procedure was used, however. In a greater number of instances, the disease progresses despite this procedure and the symptoms return, resection finally being necessary. Numerous authors believe that a short-circuiting operation *per se* is dangerous and insufficient because it leaves behind the area of diseased bowel as a source of infection and extension of the disease process. The observations of Holm,[115] and Estes[74] demonstrating the dilatation of a closed loop of terminal ileum left in the abdomen, make it desirable to resect completely the diseased segment of the bowel. Holm states that the side-tracked ileal loop of a lateral ileostomy or ileocolostomy for obstruction of the terminal ileum is likely to become elongated, dilated and ulcerated, and that an enterocolitis with mucosal degeneration will develop. Therefore, he recommends that wherever possible a resection should be done either primarily or at a second operation.

An interesting observation has been made by Pemberton and Brown[202] concerning the results which they obtained in some of their patients, employing the short-circuiting type of operation. In 3 of their cases a deficiency syndrome developed with the blood picture of primary pernicious anemia. It was not possible to determine whether the anemia was related in any way to the ileitis. In another case, they noted the development after operation of a deficiency disturbance comparable to the wet variety of beriberi. This condition disappeared with proper diet and vitamin B therapy.

On the other hand, a resection of the diseased portion of intestine has completely relieved all symptoms in 67.9% of patients in whom this procedure was employed. Because of the better results with resection, and because of the great risk of further spread if the diseased portion of intestine is not removed, a resection is the treatment of choice in the chronic stages of regional ileitis. Some discussion has arisen as to the choice of a one- or two-stage procedure. Berg[21] and others[32,42,285] recommend a two-stage resection because the latter is associated with a lower risk, because the two-stage resection may be less difficult technically, and because there may possibly develop some local immunity on the part of the peritoneum and other tissues after the first stage.

The importance of a wide resection cannot be overemphasized, since recurrence of symptoms after too conservative resection, in which portions of the diseased bowel had been left in place, has not uncommonly been reported.[61,108,123,138,244] Oppenheimer[196] suggests that the ileum should be divided at least 12 inches proximal to the visible or palpable enlargement. In addition, the entire small intestine should be carefully inspected to exclude the possibility of "skip" areas which may lie between segments of normal small intestines.

Terminology. Numerous names have been suggested and applied to this disease with the result that the nomenclature at the present time is confused by a multiplicity of varying terms—regional ileitis, regional enteritis, terminal ileitis, acute ulcerative ileitis, phlegmon of the ileum, non-specific ileocolitis, ulcerative ileocolitis, regional ulcerative enterocolitis, ileocecal pseudotumor, chronic cicatrizing enteritis, ulcerous stenosing inflammation of the lower ileum, non-specific intestinal

granuloma, Crohn's disease. The continued use of such widely different terms must inevitably produce and further the already existing chaos in the terminology of this disease.

The original name "terminal ileitis" first given by Crohn, Ginzburg and Oppenheimer[52] when the disease was thought to be confined to the terminal ileum alone is now obviously inaccurate and misleading, as are many of the other terms which limit the disease to the ileum or its lower segment. Hence, the names regional enteritis and chronic cicatrizing enteritis were suggested by others.[111] These terms, however, are for the most part merely descriptive of the region of the bowel in which the disease process may occur and give no adequate information as to the nature of the lesion. Such vague terms as pseudotumor and Crohn's disease are equally undesirable, since the names signify nothing. Probably the most accurate term and the one which should be universally accepted is "non-specific inflammatory granuloma," specifying the region of intestine involved. The adoption and universal usage of the latter nomenclature would avoid the innumerable synonyms and at the same time give the surgeon a thumb-nail description of the pathologic nature of the disease.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF

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VITAMIN A AND NIGHT BLINDNESS.

Although a disturbance of the light sense (night blindness) was reported as early as 1500 B.C. and frequent observations were made of its association with malnutrition during the latter part of the 19th and first part of the 20th centuries, the etiologic relationship was not established until 1925 when Holm demonstrated that rats, after eating a vitamin A deficient diet for 3 weeks, became night blind. The work of Holm has been repeatedly verified. Since then it has been demonstrated that the concentration of visual purple in the retinas of frogs, rats and dogs suffering from severe vitamin A deficiency is very low and may not be present at all. Severe cases of night blindness may be cured by adding vitamin A to the diet. Insofar as is known, vitamin A and its precursors are the only dietary constituents that will produce this effect.

Vitamin A and Dark Adaptation. Wald[45a,b] studied the relationship of dark adaptation of frog retinas to their vitamin A content. He found that retinas, when light adapted, contained more vitamin A than when dark adapted. If the retinas were removed and then completely bleached, the vitamin A content became much higher. He concluded from these experiments that vitamin A was a precursor of visual purple, which is the photosensitive substance in the dark adapted retina. At the present time Wald's conclusions are accepted by investigators who are working on the subject of dark adaptation and vitamin A deficiency.

In the living eye, but not in the isolated retina, visual purple is synthesized from vitamin A. The synthesis and bleaching of visual purple causes a destruction of the vitamin which must be replaced from the blood stream. Wald has developed a scheme which shows the relation of vitamin A to visual purple and dark adaptation.

Vitamin A—Assay and Human Requirements. Vitamin A is an alcohol composed of an ionone ring with an unsaturated side chain. It was synthesized by Kuhn and obtained in crystalline form by Holms and Corbet[19] in 1938. Of the 30 or more carotenoids, only 4 are known to be precursors of vitamin A. They are alpha, beta and gamma carotene and cryptoxanthin. These 4 compounds contain ionone rings. Beta carotene, the most important of the precursors, contains 2 rings and it has been shown that from 1 of its molecules 2 molecules of vitamin A are formed. The biologic activity of the carotenoids and vitamin A depends on the ionone ring and also on the unsaturated side chain.

Vitamin A can be assayed by three methods, namely, chemical, spectroscopic and biologic. In the past there has been considerable discrepancy in values obtained by the physical and biologic methods. This discrepancy may depend on whether the biologic assay is carried out by feeding saponified or non-saponified material. Better absorption of the vitamin or carotene occurs when they are in the form of esters and, therefore, the saponified material produces greater biologic effect.

Guilberg, Miller and Hughes[13] describe an experiment in which they determined the minimum amount of vitamin A and carotene required to prevent night blindness. Cattle, sheep, swine and rats showed approximately the same requirements per kilogram of body weight. This indicates that the vitamin is concerned with the general metabolic activities of the body as a whole.

The human requirement of vitamin A has not been definitely determined. Estimates that have been made are based on the work of Jeans and Zentmire,[21a,b] who used a photometer in making a test of the light sense of a group of school children in Iowa. The children with low powers of dark adaptation were given vitamin A concentrates and their powers of dark adaptation improved. Assuming the premise that the smallest amount of vitamin A necessary to prevent a decrease in the rates of dark adaptation is the minimum requirement, various standards have been stated as follows: Jeghers,[22] 6000 I. U.; Stiebeling,[41] 4200 to 5600 I. U.; Edmund and Clemmensen,[7] 700 to 900 units. The league of Nations Committee[25] recommends 2000 to 4000 I. U.

The sensitivity of the retina automatically accommodates itself, within very wide limits, to the intensity of the stimulating light by a process of adaptation. It is a well-known fact that, on passing from a lighted to a darkened room, vision is reduced for a short time and soon becomes greatly improved. The process by which the vision is increased is called dark adaptation. Conversely, the improvement of vision occurring after exposure to a dazzling light is called light adaptation.

Night blindness, which is a condition in which vision is good in ordinary light but poor in dim illumination, results from a defect in the

process of dark adaptation. It was shown to be a quantitative defect in the light sense by accurate measurements of the light thresholds made by Piper in 1903. Aubert (quoted by Adams) (1865) was the first to study the course of dark adaptation but his methods were crude.

Methods of Testing Light Sensitivity. The light sense may be tested by the following methods: 1, Determination of the light minimum by means of a photometer; 2, determination of the visual acuity in low illumination; 3, examination of the visual fields in low illumination; and, 4, determination of the power of distinction in low illumination. The first method is the one of choice because the others test the form sense as well as the light sense.

A determination of the light threshold made with a photometer represents a measure of the sensitivity of a certain area of the retina after a definite period of dark adaptation. If a series of light thresholds of a retinal area are plotted, using the duration of dark adaptation as abscissæ, a series of points will be obtained which, when connected, form a curve. The curve represents the change of the light threshold of the retinal area during a period of dark adaptation.

The actual change only of the intensities will be shown if one uses the actual intensities of the light thresholds in plotting the curve. However, by using the logarithms of the intensity of light thresholds as the ordinates, the curve will show the relative rate of change of the intensities. For example, suppose that after a specified period of time the light threshold decreased from 10,000 to 1000 micromillilamberts. Such a change would represent 1 logarithm unit. Again let us suppose that in the next period of time the threshold was reduced from 1000 to 100 micromillilamberts. The change of threshold is again represented by 1 logarithm unit in the second interval of the darp adaptation. Although the threshold decreased 9000 units in the first period and in the second only 900, in each interval of dark adaptation there actually occurred a 10-fold reduction of the light threshold. It is thus seen that logarithms show the relative rates of reduction of the light threshold.

Studies of the physiology of vision by means of the photometer, the facts known about color blindness, the curve of visual acuity, the critical frequency of flicker, the differences of the latent period, after-image phenomena, the two types of luminosity curves, the differences in chemical and electrical responses in the retina, provide a wealth of information to show that there are two mechanisms of vision. One is subserved by the rods and the other by the cones. The theory of vision, known as the duplicity theory, has an anatomic basis which was first provided in 1866 by Max Schultz. Its acceptance dates from its exposition by von Kries (1896). The essential feature of the duplicity theory is that there are two distinct types of activity in the retina: 1, A scotopic mechanism which is mediated by the rods with which visual purple is closely associated. It is concerned with the appreciation of light and movement. The perceptions are achromatic, are activated by a low threshold intensity of stimulus and, therefore typically evident in conditions of dark adaptation. 2, A photopic mechanism mediated by the cones, which concerns itself with form vision and color vision and which, with a relatively high threshold stimulus intensity, is typically evident in the light adapted eye.

As far as is known, visual purple has been found only in the rods of

the retina. But the failure to recognize it in the cones may be due to its great dilution. Visual purple is bleached by exposure to light and regeneration occurs in the dark. Regeneration is independent of the central nervous system, since it occurs even after the section of the optic nerve. Regeneration is retarded by a deficiency of vitamin A, a circumstance which is probably an important factor in the etiology of night blindness.

Anomalies of the Light Sense. Anomalies of the light sense may be divided into 6 categories as follows:

1. *Result of disease of the eye*—peripheral lens opacities and disease of the periphery of the retina, such as pigmentary degeneration, advanced myopia and chorioretinitis, which affect the periphery more than the fovea. A related failure in adaptation may occur in retinal detachment, optic neuritis and glaucoma.

2. *As a congenital and hereditary condition.* Simple congenital night blindness may occur without any associate anomaly. There may be three tendencies in its hereditary transmission: *a*, A dominate form which was first noted by Cunier (1838), who started the compilation of the famous pedigree of Jen Nougaret, the largest pedigree known for the inheritance of any human condition; *b*, a recessive form, frequently associated with myopia; and, *c*, a recessive sex-linked form, usually associated with a high grade of myopia. This form is transmitted through unaffected daughters of affected males to some of their sons.

3. *Congenital and hereditary night blindness* associated with other anomalies of the retina, such as in Oguchi's disease, and in various types of pigmentary degeneration of the retina.

4. *Pathologic changes in the liver* have been associated with the etiology of night blindness and it forms an occasional symptom of jaundice.

5. The factor of *overexposure to light.* Aykroyd[2a,b,c] reported this phenomenon and associated it with vitamin A deficiency.

6. Cases in which *no pathologic changes* are evident and nutritional disturbances have been absent. The majority of these have been associated with neurasthenic and other functional symptoms.

Recent Investigations by Photometric Methods. Photometers have been known for almost half a century and, as early as 1896 were used to study the light thresholds of malnourished persons who had night blindness. This instrument did not become popular as a method of detecting subclinical states of vitamin A deficiency until 1934, when Jeans and Zentmire reported that, by means of the photometer, they detected a disturbance of dark adaptation in 21 % of a group of 213 children in Iowa. About one-half of the 21 % were kept in a hospital and given cod-liver oil, and, after a period averaging 12 days (4 days to 6 weeks), all showed improvement in their dark adaptation.

Other investigators have shown that the incidence of vitamin A deficiency is likely to be high if a photometer is used in making the tests. On the other hand, some investigators have not been so successful in finding a high incidence of vitamin A deficiency or even finding a correlation between the variation of photometric determinations of dark adaptation and the vitamin A content of the diets.

Recently Hecht and Mandelbaum[16] published a report of photometric

process of dark adaptation. It was shown to be a quantitative defect in the light sense by accurate measurements of the light thresholds made by Piper in 1903. Aubert (quoted by Adams) (1865) was the first to study the course of dark adaptation but his methods were crude.

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6. Cases in which *no pathologic changes* are evident and nutritional disturbances have been absent. The majority of these have been associated with neurasthenic and other functional symptoms.

Recent Investigations by Photometric Methods. Photometers have been known for almost half a century and, as early as 1896 were used to study the light thresholds of malnourished persons who had night blindness. This instrument did not become popular as a method of detecting subclinical states of vitamin A deficiency until 1934, when Jeans and Zentmire reported that, by means of the photometer, they detected a disturbance of dark adaptation in 21% of a group of 213 children in Iowa. About one-half of the 21% were kept in a hospital and given cod-liver oil, and, after a period averaging 12 days (4 days to 6 weeks), all showed improvement in their dark adaptation.

Other investigators have shown that the incidence of vitamin A deficiency is likely to be high if a photometer is used in making the tests. On the other hand, some investigators have not been so successful in finding a high incidence of vitamin A deficiency or even finding a correlation between the variation of photometric determinations of dark adaptation and the vitamin A content of the diets.

Recently Hecht and Mandelbaum[16] published a report of photometric

studies on 4 normal adults who were on vitamin A deficient diets. The subjects showed a change in the powers of dark adaptation of both the rods and cones as soon as 14 days after going on the diet. After 35 days, the threshold of the rods had increased about 1 logarithm unit while that of the cones had increased ½ logarithm unit. The light thresholds of these subjects did not return to normal after many days subsequent to the ingestion of vitamin A or its precursors but remained at high levels even after 70 days. These findings indicate that it may take longer to restore the normal functions of the rods and cones than it does to decrease them by altering the vitamin A content of the diet. These findings are not in agreement with other published results.

Wald and his associates[45,47] recently reported the results of an experiment conducted on 1 human subject in manner similar to the procedures followed by Hecht and Mandelbaum. The experimental subject developed definite changes in dark adaptation after being on the diet for 4 days. After 25 days, the threshold of the periphery of the retina had increased 1.5 logarithm units. After taking 100,000 units of vitamin A, in the form of carotene in oil in gelatin capsules, orally, the light threshold returned to normal in 38 minutes. This speed in the return of the light sense to normal values after taking vitamin A is of the same order of magnitude as that which has previously been reported, but differs greatly from the very slow rate of recovery of the subjects used by Hecht and Mandelbaum.

Experimental Results: Dermatologic Findings. Lesions of the skin occurring in conditions of malnutrition were described by Wiltshire[48] in 1919, Nicolau[31] in 1919, and Aschoff and Koch[1] in 1920. But the relation of these lesions to vitamin A deficiency was not recognized until 1931, when Frazier and Hu[10] reported a form of dermatosis occurring in soldiers who had been living on diets deficient in meats, eggs and green vegetables for periods ranging from 6 months to 2 years. These men were in their early twenties and had reported to the ophthalmologic clinic during February, March or April, 1929, because of keratomalacia.

Nicholls (quoted by Youmans and Corlette[50]) described a papular lesion on dry skins which was frequently accompanied by mild neuritis, keratomalacia or diarrhea among poorly fed laborers in East Africa and among convicts in Ceylon. Because of the roughness of the skin, he named the condition phrynoderma (toad skin). He thought that this condition may be due to other food deficiencies associated with lack of vitamin A, because some of his cases also had dysentery and neuritis.

Loewenthal described a similar dermatosis occurring in prisoners in East Africa who were also afflicted with night blindness and xerophthalmia. Treatment with cod-liver oil for 9 weeks, and without modification of the diet, resulted in cure of the night blindness and xerophthalmia in every case and of the dermatosis in 99%. The average age of the prisoners was 35 years. Loewenthal's description of the dermatosis was concerned with five features:

1. *Dryness of the skin* affecting the whole body, both sebum and sweat being deficient. This change is most marked on the extensor surfaces of the arms, on the backs of the hands and front of the legs

and on all surfaces of the thighs and across the buttocks. 2. *Itching:* a very prominent feature. 3. *Papular eruption* usually on the extensor surfaces of the arms and on the front and outer surfaces of the thighs. The papules were about 0.6 cm. in diameter and smooth-topped. The edges were sharply demarcated. 4. *Folliculitis:* in some cases there was an inflammatory swelling of the hair follicles without pus. Usually there was a broken hair projecting from the center. 5. *Acne:* clinically, the papules differ in no way from those of acne vulgaris except that pustulation is extremely rare.

Goodwin,[12] in London, and Sweet and K'Ang,[42] in China, described similar follicular keratotic lesions in association with vitamin A deficiency.

The *histopathological features*, described by Rae,[36] are very similar to those described by Frazier and Hu,[10] Loewenthal[27] and Nicholls. The description by Rae, taken almost *verbatim*, is as follows:

1. *Epidermis.* There is a superficial hyperkeratosis of the epidermis in all cases. In some places the stratum corneum was very much broadened. There was no evidence of parakeratosis. The keratin was either homogeneous in structure or present in loose meshes. No appreciable changes were present in the stratum lucidum and the stratum granulosum. The rete mucosum in some places, especially in the neighborhood of the atrophied hair follicles, showed moderate hypertrophy. The interpapillary processes were widened and more prominent in these areas. The prickle cells appeared normal but, in places, showed vacuolation in their protoplasm. The cells of the stratum germinativum were apparently normal. Evidence of hyperpigmentation was not marked even in the neighborhood of the papules.

2. *Corneum.* Except for changes in the perifollicular regions, the corneum was apparently normal.

3. *Sebaceous Glands.* The sebaceous glands are not seen in connection with the atrophied hair follicles. Serial sections, however, revealed that the glands were still present in some areas in which the follicular lesions were not very marked. In these areas there was a varying degree of hyperkeratinization of the lining epithelium of the hair follicles. The sebaceous glands showed either a decrease in the amount of cytoplasm or in the number of cells. At a later stage of the follicular lesion, a few cells with very little cytoplasm represented the glands. In typical papules they were atrophied and their site was generally occupied by young connective tissue and mononuclear lymphoid cells.

4. *Sweat Glands.* Changes in the sweat glands were not a marked feature. In some instances, however, the coil glands were few in number, their epithelium was flattened or shrunken and irregular and the lumen dilated. The funnel-like depressions in the epidermis containing the sweat pores were filled to a varying extent with the hyperkeratinous material.

5. *Hair Follicles and Hair.* Marked changes were found in the hair follicles in all instances. The number of follicles affected and the degree of changes present, however, varied. The mouths of the hair follicles showed marked hyperkeratinization of the living epithelium and, as a result, the funnels of the follicles were widened and were plugged by dense masses of horny tissue. Closer examination revealed that the

follicular plugs consisted of concentric lamellæ of flattened cornified cells in which there were no nuclei. In 1 case, instead of the filter-like depression, slight or marked elevations were often found at the mouths of the affected follicles. Sections of the coiled and atrophic hairs or broken hairs were seen in the substance of some of the follicular plugs but pustulation in the latter was not noted in any instance. Serial sections showed that the lower part of the affected follicles was atrophic and was often separated from the upper part of the follicles by delicate fibrous tissue. In some places, however, the lower third of the follicles showed moderate hypertrophy of the external root sheath.

Varying degrees of cellular infiltration, mostly fibroblasts and mononuclear lymphoid cells, were often present in the loose perifollicular tissue; neutrophils, eosinophils and evidences of hemorrhage were not noticed in any instance.

The papules, which constitute the important clinical manifestation of the skin lesions in vitamin A deficiency, arise from the pilosebaceous follicles as a result of non-inflammatory hyperkeratosis of the lining epithelium. The perifollicular infiltration is probably secondary to the irritation of the keratotic plug in the orifice of the hair follicle.

The atrophy of the sebaceous glands is secondary to the plugging of their ducts by keratotic epithelium. However, the absence of sebaceous cysts in all instances would suggest that, apart from the mechanical factor, the nutritional deficiency is also primarily responsible for the atrophy of the sebaceous glands.

A number of other conditions have been described. These include ichthyosis follicularis, lichen planopilaris, pityriasis rubra piloris, keratosis suprafollicularis, lichen spinulosus, characterized by the presence of horny plugs at the orifices of the hair follicles forming small papules.

Rae states that phrynoderma is a separate entity associated with malnutritional states. No experimental evidence has been produced to show that it is definitely due to deficiency of vitamin A alone, since similar changes in the sebaceous glands have been noted in combined deficiencies of vitamins A and B, and also in scurvy by several investigators.

Youmans and Corlette[50] reported that 6 of the 20 cases of dermatosis they studied showed skin lesions similar to those described above. They also observed that the lesions disappeared when the patient was given cod-liver oil. Photometric studies of some of their patients demonstrated an occasional mild hemeralopia. However, they thought that in some instances the skin lesions may be among the first clinical evidences of vitamin A deficiency.

Vitamin A deficiency produces pathologic changes in many other organs. Most of the changes consist of a keratinizing metaplasia in which epithelium, regardless of its location or function (*i. e.*, bronchi, genito-urinary tract, salivary glands, or stomach and intestines) is replaced by stratified keratinizing epithelium. The first change in the epithelium is atrophy. This is then followed by proliferation of the basal cells to form stratified keratinizing epithelium. This metaplasia is identical in appearance in all locations.

In the rat, the salivary glands and respiratory tract are affected first. The genito-urinary tracts are next involved, and last to be affected are the ocular and paraocular tissues. Administration of vitamin A to

these deficient animals will effect a reversal of the metaplasia and, for some reason, repair is more rapid with butter fat than cod-liver oil. Wolbach and Howe[49] did not believe that infection was more common in rats deficient in vitamin A but did think that, once infection was started, the process of epithelial repair was retarded. When repair of the epithelium started it was diffuse and sudden, due to the fact that all cells were capable of proliferation. If repair of the epithelium starts before metaplasia is complete, that is, after the original epithelium has been undermined by an epithelium of basal cell origin but not yet developing keratinizing epithelium, it will be completed in from 5 to 13 days. When the metaplasia has been completed and new stratified squamous keratinizing epithelium is laid down comparable layer by layer with the epidermis, repair is complete in 10 to 12 days, but the repair is not in the same stage at all places. The repair of epithelium which is normally either stratified or of the transitional type, as in the conjunctiva or bladder, is complete in 7 to 8 days.

Johnson conducted experiments on rats and found that severe vitamin A deficiency produced degeneration involving several layers of the retina which is probably not reparable. Hart and Guilbert reported cases of night blindness in cattle and sheep resulting from severe avitaminosis A which was permanent, although ample amounts of vitamin A were administered for months in an attempt to cure the visual defect.

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